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PERIBRONCHIAL TUBERCULOSIS OF THE LUNGS

WITH SPECIAL REFERENCE TO THE IMPORTANCE OF THE HILUM

A Review

JAMES A. HONEIJ

Boston

The subject of this paper affords an excellent illustration of the rapid advance medical science takes in certain directions, due to a particular discovery. In this case the discovery of X-rays, and their application to diseases of the chest, has considerably advanced and also modified our ideas and knowledge of thoracic processes. The frequent renewed interest in tuberculosis—a new conception of a primary lesion, of the course of progress or regress and of functional changes—is largely due to roentgenological studies during the last twelve years.

From general study and application of the X-rays to thoracic conditions we have reached that more interesting stage of specifically applying our knowledge in detail to definite portions of the thoracic contents.

The present review and study concern especially that more or less vague area which we commonly term the hilum.

The literature on this specific question is so enormous that only those articles have been quoted which add to or definitely modify our point of view, and especially clarify our conception of diseases of the hilum.

The importance of the study of the hilum has been emphasized ever since radiographic examination proved that tuberculosis of the tissues in and around it frequently preceded processes elsewhere in the lungs. In children, for instance, the primary appearance of pulmonary tuberculosis appears to have its most common starting point in the hilum. The question, therefore, can be studied or approached in several ways. Here the question has been studied in the following manner:

a. The cause, type and degree of reaction;
b. The position and general appearance of the hilum, with
c. The associated changes and
d. The end results.

Many years ago it became an accepted fact that there was no pulmonary affection which did not also affect the lymphatic nodes. Ghon was influenced in this respect largely because of the fact that infection of the nodes was believed to occur secondarily and because the lymph flow was toward the hilum. Ghon therefore has been the outstanding opponent of the theory of primary lymph node infection. This has been accepted and written into every text book.

The question of tuberculosis of the tracheobronchial lymph nodes, and whether they were primarily infected, has since been broadly argued by most pathologists.

An editorial appearing in 1899 probably reflects the opinion of the time when it states that "Tuberculosis does not as a rule occur primarily in the parenchyma of the lung, but has its beginning in the glandular and lymphatic structures of the respiratory or digestive apparatus. . . . . The lung affection represents an extension from a glandular or lymphatic focus, which has broken down."

Ribadeau-Dumas, Albert Weill and Maingot have confirmed the theory of Rist and Ribadeau-Dumas, showing that tuberculosis of infants ordinarily begins as a small focus in the lower lobe, then attacks the nodes of the hilum, and then the tracheobronchial nodes, and affects the apices only subsequent to these lymph node lesions.

Engel reports a case of bronchial node tuberculosis in a child eight months old, with the primary nodule in the right upper pulmonary lobe.

Authorities have believed that in every case the entrance of tubercle bacilli with its primary manifestation corresponds to the point of invasion and swelling of lymph nodes (Baumgarten, Cornet).

There are of course exceptions to this rule. Pirquet is by no means convincing when he says that "we have no accurate knowledge as to the duration of the primary stage of lymphatic gland infection." "This primary infection," he says, "with a termination into nonapparent, nonperceived tuberculosis of the lymph glands has this advantage, that the organism enjoys a certain, though incomplete, immunity against renewed infection." It is a question, whether Pirquet recognizes primary gland tuberculosis. It is well known that before authorities accepted a primary lymph node tuberculosis, many believed that the lymphatic system could be primarily infected before the pulmonary parenchyma was touched.

Koch agrees with Ghon that the primary lesion is in the lung and then spreads through lymphatics to regional lymphatic nodes. In discussing

the relation of the pulmonary focus to lesions in regional lymphatic nodes, Opie states that the most conspicuous character of tuberculosis in children is the extent of involvement of the regional lymphatic nodes.

The susceptibility of the lymphatic nodes of infants and very young children to tuberculosis is well shown, Opie says, "by great enlargement and widespread caseation of the affected nodes. Masses of greatly enlarged, almost wholly caseous lymphatic nodes occupy the hilum of the lung in which the pulmonary focus is situated, and similar masses fill the spaces between trachea and lung or the angle at the bifurcation of the trachea."

In adults, continues Opie, "Pulmonary tuberculosis almost invariably affects the apices of the lungs—the disease does not implicate the regional lymphatic nodes at the hilum of the diseased lung."

Sluka, in describing the hilum lesion as an infiltration and not as a primary pulmonary nodule, states that the localization of the primary pulmonary focus does not conform to any definite rule.

Many investigators have seen the difficulty of determining the primary lesion because of the fact that the mucous membrane can be penetrated without leaving behind a demonstrable lesion. Wright, for instance, states that "We must assume at present (1901) that the tubercle bacillus passes into the lymphatics through the mucous membrane of the naso- and oro-pharynx in a very large proportion of the cases of pulmonary infection."

Ravenel states reassuringly, on the other hand, that, "when death has occurred from other causes, the tuberculous lesion is usually localized and often confined to the glands which are in relation to the point of invasion, hence the portal of entry can be determined with great certainty."

As regards the site of early tuberculous infection Adami and McCrae show in their series of cases that the thoracic nodes were affected in 33 per cent, which is second in frequency to the infection of the lungs. In another group of generalized tuberculosis, the lungs were involved in 95 per cent of the cases and the lymph nodes in 81 per cent; of this number all but two cases were in the thoracic nodes.

It is reasonable to believe, Harbitz says, that tubercle bacilli may pass through one or more groups of lymph nodes before becoming stationary and setting up inflammation; he supports this view by the results of certain feeding experiments in which the thoracic nodes have been found to be tuberculous without corresponding disease of the glands in the

abdomen. Harbitz considers it certain that in some cases primary tuberculosis occurs in the lymph nodes.

In 1909 it was being debated whether pulmonary tuberculosis in adults could be traced to some remote tuberculous process that existed previously, namely, in the lymph nodes of children.

In respect to this last statement it is of interest to quote Ranke who, in reporting the autopsy findings in a case of tuberculosis in a man 72 years of age, states in part that the lung findings are in all respects analogous to the primary lung lymph node tuberculosis of children. The changes resemble primary tuberculosis in a child, in that the size of the primary lesion is many times smaller than the total tuberculous changes in the nodes. Harbitz concludes that primary tuberculosis of lymph nodes is quite frequent in adults, but also emphasizes latent tuberculosis.

Before leaving the question, as it was considered up to 1910, I should like to quote Tendeloo who states emphatically that if there is tuberculosis of the bronchial nodes without tuberculosis elsewhere it has occurred from the bacilli coming from the lung. He also states more precisely that the primary foci occur most in the peribronchial, perivascular tissue; concluding, however, that it is possible that bacilli go from the pulmonary lymphatics either directly or after having infected one or more peribronchial lymphatic nodes, then from these nodes elsewhere in the lung lymphatics.

Thus, in 1911, for instance, Hartley and Powell apparently still reflect the opinion that tuberculosis of the hilum nodes cannot be accepted as an entity. They publish a table showing a collection of 1,066 cases of children and adults, in which is given the type of bacilli causing infection and the type of tuberculosis produced. In this table there is no mention of tuberculosis of the lymph nodes or tissues of the hilum region—I mean hilum region in the broadest sense.

Norris and Landis also record their disbelief, by stating that "the proportion of cases in which the apex is the primary site of the disease is so large that, generally speaking, the exceptions can be disregarded."

After reviewing a portion of the enormous literature of this particular phase of the question up to 1910–1911, the decided impression is obtained that hilum node tuberculosis was not known or accepted as an entity, although the opinion was being emphasized that pulmonary lymphatic tuberculosis did occur; by some that it was primary and by others that it was secondary to a pulmonary lesion. Some authorities were out-

spoken, and stated that, if it occurred as a primary lesion, it was rare and not of as much importance as pulmonary or intestinal tuberculosis.

The second phase of the question to be studied is the acceptance and diagnosis of tuberculosis of the lymph nodes of the hilum area. D'Espine's contribution in 1907 had much to do in focusing our interest. He believed that enlarged bronchial nodes were tuberculous and gave rise to physical signs, determined by auscultation, over the seventh cervical and first dorsal vertebrae. In a number of nontuberculous cases (bronchopneumonia with measles and four cases of grippe) this sign was also obtained but autopsy showed that in some cases an adenopathy was present. In these cases, however, the sign should persist for six months or more to be considered as evidence of tuberculosis. Credit for first diagnosing tuberculosis of the bronchial nodes by roentgen rays is given to De la Camp and Kohler (1904–1906) by Assmann.

The postmortem reports on the distribution of the lesion and the frequency with which the lymph nodes of the hilum region were found to be affected, especially in children, with and without associated pulmonary foci, further directed attention clinically and roentgenologically to this question. Cornet quotes Mueller, who, in postmortem examinations of 500 children under 15 years of age, found the lymph nodes involved 126 times and the bronchial nodes 103 times. Neumann, also quoted by Cornet, found, in the examination of 142 cases of children 15 years of age and under, that in 46 there was tuberculosis of the lymph nodes. Babes, quoted by Harbitz, found in 902 postmortems in children under 15 years of age, dying from acute infections, tuberculosis in 288 cases or 31.9 per cent and always in the lymph nodes. Harbitz is also of opinion that lymphatic tuberculosis changes to pulmonary tuberculosis when children reach the age of 15 years.

Adami and McCrae (1908) reported that in 151 cases of healed tuberculosis the thoracic lymph nodes were involved in 45 cases and in these the group of nodes at the lung root predominated 38 times, and when only a single site was found it was 23 times in the lung root group. In another series of 93 latent tuberculosis cases the thoracic nodes were involved 35 times, and 18 times in combination with pulmonary lesions.

In studying postmortem the distribution of tuberculous lesions in 185 children under three years of age, Wollstein found, among other facts, that in 13 cases the lungs and bronchial nodes were alone involved and in 1 case the bronchial lymph nodes were alone involved. Considering

the bronchial nodes alone, there occurred in 131 cases tubercles with cheesy degeneration. In 38 cases the mediastinal lymph nodes were markedly affected. Again, in 1921, Wollstein and Spence report their study of tuberculosis in infants and young children (6 weeks to 5 years) with findings, in part, as follows: In a series of 362 children with 184 necropsies they state that "in some of these cases the oldest lesion was found in the lungs (74 cases), in others in the bronchial glands (57 cases), and in still others the lesions in the lungs and in the glands seemed to be about the same (36 cases). There was no instance in which the lung alone was the seat of a tuberculous lesion" and "in no instance were the bronchial glands alone affected." These investigators state that in no case of the 184 necropsies was there evidence of a healed tuberculosis.

Harbitz's findings are interesting in contrast. He gives the following table:

Primary lesion in respiratory tract	in 48 cases, or 41.0 per cent
Primary lesion in digestive tract	in 26 cases, or 22.0 per cent
Primary lesion in respiratory or digestive tract	in 24 cases, or 20.5 per cent
General lymph node tuberculosis	in 11 cases, or 9.4 per cent
Doubtful	in 8 cases, or 6.8 per cent

Harbitz called attention, however, to the frequency of latent lymph node tuberculosis in children, reporting also that the postmortem findings of 275 children showed tuberculosis in 42 per cent and that a large proportion of this number had the primary lesion there.

Hamburger and Sluka, presenting 110 cases of tuberculosis, showed that 62 had enlarged bronchial lymph nodes on both sides, 40 on the right and 8 on the left side. The lungs were affected in 63 cases, and when the lungs on the right or left were affected, lymph nodes on that side were also affected.

Opie and Andersen, although presenting statistical data, state that the early focal lesion has the character of the first infection and implicates the lymphatic nodes, whereas the apical lesion has the character of a second infection. This last opinion has been expressed by a number of investigators. But Opie and Andersen add that this apical lesion exhibits no tendency to cause caseous tuberculosis of adjacent lymph nodes.

Birch-Hirschfeld gives the results of the examination of 3,067 sections, in which 41.86 per cent showed tuberculosis and 24.3 per cent in which tuberculosis was the cause of death. In this series he was able to demonstrate the healed pulmonary nodule in 11.97 per cent and latent or not

completely latent, nodular pulmonary tuberculosis in 2.8 per cent. He also describes 28 cases of initial bronchitic tuberculosis.

Roberts thinks that there is no reason to doubt the primary affection of the lymph nodes, but adds, however, that there may be a question of predisposition and that it is a question whether these nodes represent the remains of a previous infection or the early stage of a present disease.

Sufficient evidence has been frequently presented to show that foci in the lungs present many characteristics of secondary infection of the lungs, as also that the hilum nodes present many characteristics of primary infection. "In many cases we find the apices of the lungs free from disease. Above all, we further know, through the anatomical findings, that pulmonary tuberculosis of children and young people begins in the lymph nodes at the hilum of the lungs" (Krause). Hart states that, with rare exception, an initial apical tuberculosis does not occur in children.

Czerny (quoted by v. Ohlen) stated many years previously, however, that there is no hilum gland tuberculosis without pulmonary tuberculosis and Ghon, as has been stated, believes in aspiration tuberculosis and that bacilli do not pass through the lungs and cause changes in the lymph tissue and surroundings. To-day many authorities believe that the frequency with which tuberculosis of the hilum occurs in children is comparable to the frequency of apical tuberculosis in adults. Fisher believes that hilum tuberculosis in the adult is rare and that it is equally rare to find chronic tuberculosis in children. A chronic disease, he states, is invariably nontuberculous in children. Barjon states that the existence of tracheobronchial adenopathy is very common in adults as well as in children. Elsewhere Barjon states, "there are even cases in which tuberculosis of the hilum precedes pulmonary tuberculosis." "This mode of onset," he says, "is admitted by a large number of clinicians. In adults it is much disputed." For this same opinion, however, we can refer to Rieder, who in 1908 insisted on lesions of the hilum and their extension upwards.

"Caseation of the bronchial glands is not a specific character of childhood but of primary tuberculous infection. If, on the other hand, pulmonary tuberculosis of the adult is, as a rule, not accompanied by caseation of the corresponding bronchial glands, it is not because the lymph glands of the adult are essentially and physiologically different from those of the child, but simply because pulmonary tuberculosis of the adult is due to a re-infection" (Rist).

Hamburger states that "with few exceptions cases of bronchial lymph node tuberculosis which lead to true symptoms of disease are confined to the first and second year." Philippi goes further and says, "it must be remembered that only rarely, especially in adults, is it purely a glandular process; rather is it a more or less pronounced disease of the surrounding hilum tissue in the form of peribronchial and infiltrative processes of the neighboring pulmonary tissues."

It can be accepted that postmortem statistics show about an equal percentage of incidence in pulmonary and tracheobronchial lymph node tuberculous involvement in children. Many single cases are reported, both in adults and in children, of tuberculosis of the hilum nodes. Gerstl, for instance, reports a case of hilum node tuberculosis on the right side, in an infant 21 days old, who gave physical signs, positive tuberculin reaction and X-ray proof. Riviere, at the other extreme, presents a case of a man twenty-four years of age, giving paravertebral dulness and X-ray evidence of hilum tuberculosis in the adult. This writer also believes that hilum tuberculosis is commonly a peribronchial disease with a chronic and intermittent course.

In a review of tuberculosis in children, covering twenty-one years of work, Shennan reports the findings of 1,085 postmortems, 68 per cent of which were in children under five years of age and none under one year of age. He states that the "lymphatic glands were tuberculous in 92.4 per cent in the first series and in 78.8 per cent in the second series. The mediastinal nodes were more frequently affected than the abdominal nodes, and dissemination took place more frequently, apparently, from the former group." He further states that "tuberculosis of the mediastinal glands was commonly unaccompanied by primary tuberculosis of the lungs, but was frequently accompanied by recent tuberculosis of these organs, in many cases evidently secondary to the gland tuberculosis."

Much states that "in the majority of cases the bronchial glands represent the first site of invasion and localization for the bacilli." Hektoen states that "it is highly interesting to note that in children tuberculous infection of the lungs probably most commonly results from the rupture of foci in the bronchial nodes into a large bronchus, generally near the hilum." Ghon, whose opinion has already been given, found in 169 cases 30, or 17.75 per cent, in which there was evidence of a breaking through into the bronchus from a lymph node.

Baréty in 1874 in reviewing the literature reports case after case in infants and adults of tuberculosis of the tracheobronchial and mediastinal lymph nodes.

From what has been said on the question thus far, we can assume that tuberculosis of the hilum nodes does occur, that it occurs more commonly in children, that the incidence is anywhere from 40 to 70 per cent, that it has primary manifestations, that it is an acute condition and may be of serious importance. Furthermore, hilum node tuberculosis occurs without and with pulmonary disease. But after reviewing the literature, one is discouraged to find that in many textbooks on diseases of the lungs no mention is made of hilum lymph node tuberculosis.

If we consider the importance of the question in relation to its latent factor and the recognition it received a half century and more ago, as is demonstrated by that remarkable piece of work on *De l'adenopathie tracheo-bronchique* by Baréty in 1874, this present day neglect is discouraging.

Before concluding, reference to conditions with more or less similar pulmonary findings is justified. Irvine and Watt, in their study of miners' phthisis, point out that the irritation caused by dust practically operates at all points in the lungs. But it shows its effects particularly in "those portions of the lungs whose range of movement in respiration is least, namely in the posterior portions, and round the root of the lung. The dust having penetrated the walls of the alveoli is carried further by the lymphatics. The distribution of these is around and along the bronchioles and blood vessels, in the interalveolar tissue, along the interlobular septa, and under the pleura, all converging to the root of the lung and bronchial glands."

In malignant disease we get a comparative condition. Hebert points out with what ease invasion of the lymphatics takes place in primary mediastinal sarcoma and its extension from the pulmonary lymph nodes along peribronchial lymphatics to the next node. Hebert presents an excellent topography to bear out his assertions.

Personally, I have gone on the assumption that the greater proportion of cases of tuberculosis in children were infected by way of the lymphatic system, largely because this seemed most logical, and because of the impression made on me by von Behring's work. Since 1908, the occurrence of a thoracic lymphatic tuberculosis, primarily in infancy and later manifesting itself in the mediastinal nodes, turned my attention in this direction. The result of this was a report on *The Importance of Medi-*

astinal Glands published in 1911. Since then (1918) I have emphasized the significance of the hilum, when interpreting radiographs in certain pulmonary conditions, but especially in pulmonary tuberculosis.

In closing this part of the paper attention is drawn to the significance, pathologically, of the changes in the lymphatics and nodes in the hilum region. Pathologically, it is obvious that in considering enlarged lymph nodes which occur in the thorax we are dealing with no special disease. In all likelihood, tuberculosis is in the majority of cases responsible for their enlargement. But the nodes alone may be involved, either in an acute or subacute stage, or inflammation of neighboring structures may have been extended to them. After reviewing the subject, a question difficult to determine pathologically is where and when does hilum tuberculosis terminate and pulmonary tuberculosis begin?

The point to consider next is the relation of the hilum to peribronchial conditions. Radicles of the peribronchial lymphatics being included in the tuberculous area, the bacilli easily find their way into the lymph vessels, and peribronchial tuberculous lymphangitis results. This Hektoen believes and further describes, "The tubercles sometimes running around the bronchi like a string of beads, and now extension may take place to the bronchial walls or to adjacent alveoli." "Occasionally," Hektoen says, "the process can be followed as peribronchial nodular cords clear to the lymph nodes at the hilum."

This particular picture has been described by numerous investigators and is to be borne in mind when the roentgenographic evidence is considered later on. Calmette, quoted by Ravenel, considers the question of peribronchial lymphatic infection in greater detail. "Leucocytes," says Calmette, "which have englobed only one or two bacilli retain for a time their mobility, and when arrested in the capillaries, penetrate the vessel walls by diapedesis, reaching the lymphatic channels which carry them to the bronchial or mediastinal glands."

This opinion conveys, however, the fact that Calmette considers hilum secondary to pulmonary infection. This point of argument has already been generally considered, but can be taken up in particular as an explanation of tuberculosis of the hilum as a primary process, and tuberculosis of the peribronchial lymphatics as a secondary process.

Harbitz, quoted by Hektoen, considers it likely that in children "tuberculosis of the lungs often develops as a result of retrograde infection from the tracheobronchial lymph nodes" because he found tubercles in

these nodes frequently without involvement of the lungs, but the reverse very rarely.

Gittings states that on anatomic grounds it is difficult to see how infection could travel through the lymphatics in a retrograde direction on account of the valves; but in reality he gives an obvious reason for such infection, for he says "only in the event that the lymphatic channels are blocked or compressed would the tubercle bacilli be likely to involve the channels themselves and thus favor retrograde infection toward the lungs." This opinion is held by Hebert and Gouldesbrough, who suggest that the origin of a parenchymal focus is brought about in the following manner:

> When tuberculosis develops in a hilum gland which receives a bronchial vessel, the resulting inflammation tends to obstruct that vessel. The lymph finds a new outlet and passes by means of anastomosis into neighboring vessels. The lymph flow in the section between the gland and the anastomatic area is therefore reversed. Any tubercle bacilli escaping from the affected gland travel outward. On reaching the relatively narrow anastomosing vessels, they may be arrested and give rise to tubercles in the lung parenchyma.

Hektoen, in speaking of tuberculous bronchopneumonia occurring most frequently in children after certain acute infectious diseases, states that "in such cases the peribronchial lymph nodes are usually large and caseous, and frequently the invasion of the lungs follows rupture of a tuberculous node into a large bronchus near the hilum."

"Although the first extension from the hilum is peribronchial," says Bushnell, "after the period of manifest tuberculosis is reached, peribronchial extensions are almost always secondary to superficial and more or less circumscribed lesions." Assmann recognizes peribronchial tuberculosis, which, he says, gives rise most often to a bronchopneumonic process.

In the Surgeon General's *Circular No. 20*, which was used as a guide during the war in the examination of men for pulmonary tuberculosis, there appears the following which apparently was a consensus of opinion at that time:

> Tuberculosis of the bronchial glands is a diagnosis often made from the radiograph on very slight foundation. The fact is that pronounced swelling of the lymph glands is characteristic of primary, not of advanced tuberculosis. It is rare that intrathoracic gland tuberculosis is of any clinical importance in the adult. Only rarely, especially in adults, is so called hilum gland

tuberculosis a purely glandular process; it is rather a more or less pronounced disease of the surrounding hilum tissue in the form of peribronchial and infiltrative processes of the neighboring pulmonary tissues.

Our present day observations, however, are by no means new. LeRoy de Mericourt (quoted by Baréty) for instance, reported a case in 1860 (which was also diagnosed during life) of bronchial phthisis or peribronchial adenitis, which showed an absence of tubercles in the pulmonary parenchyma.

Tendeloo precisely states that the primary foci occur most in the peribronchial, perivascular tissue; concluding, however, that it is possible that bacilli go from the pulmonary lymphatics either directly or after having infected one or more peribronchial lymphatic glands, then from these lymph nodes elsewhere in the lung lymphatics.

Before considering as logical the assumption of a peribronchial lymphatic tuberculosis it will be interesting to review the anatomic basis for such deduction.

Miller has shown in a valuable series of painstaking work the distribution and importance of lymphatics and lymphatic tissue, and every student of pulmonary disease should appreciate the value of this study in the diagnosis, especially, of hilum and peribronchial tuberculosis.

Miller shows that the bronchi and the pulmonary arteries and veins are abundantly supplied with a network and with main branches of lymphatics. In the pleura there is also a rich network of lymphatics which communicate with the deep pulmonary lymphatics. At the divisions of the bronchi, in their angle, lymphoid tissue is found and along the large divisions of the bronchial tree true lymph nodes have been described. Miller emphasizes an important fact in regard to the lymph flow. He states that the lymphatics of the bronchi, arteries, the main venous trunks and the greater part of the pleura, flow toward the hilum. But, in the lymphatics about the veins, in those vessels just beneath the pleura and which communicate with the pleural network of lymphatics, the flow may be towards the pleura. This, Miller says, probably explains why we may find tubercles in the pleura and none in the deeper part of the lung. Miller in stating that the lymph flow is towards the hilum, says

> at the hilum the lymphatics which come from the pleura, from the bronchi, from the pulmonary artery and from the pulmonary veins all drain into the various groups of lymph nodes. It is in the lymphatics about the pulmonary

veins in this region that I have encountered valves pointing towards the hilum and the lymph nodes. I have never seen lymphatics unconnected with lymph nodes passing to the lung and we know that from the lymph nodes the drainage is into the thoracic duct.

Therefore, if we have an inflammatory congestive process, such as is common in active tuberculosis, in the hilum area with enlarged lymph nodes, sufficient interference may be caused by the lymph flow to seriously impede if not prevent the direct flow of lymph toward the hilum. The infection of the lymphatic system, locally, and the extension of the process away from the hilum appear logical, and may account for the often rapid, progressive cases of peribronchial (pulmonary) tuberculosis after its primary appearance in the hilum region.

Noninflammatory processes (merely secondary enlarged glands, dormant), therefore, with noninterference of lymph flow, may also be the explanation for the adult type (chronic), which becomes activated following influenza, for instance, which numerous investigators report. Much gives this explanation when he says "another complication has to be added to the effects of influenza: the frequent swelling of the bronchial glands. It is an easy matter for bacilli to reactivate themselves in the diseased glands, or to find suitable conditions for their growth. Very often an outbreak of active tuberculosis occurs as an after-effect of influenza." These are also described by Méry. Cases such as Much describes I saw at the army tuberculosis hospital, U. S. A., No. 16, after the epidemic of 1918.

Hebert and Gouldesbrough report 6 cases of hilum tuberculosis in which the tuberculosis was confined or had spread from the tissues of the hilum. They think that in certain types of hilum disease, in which healing has taken place, active tuberculosis may arise after many years, spreading from the affected lymph nodes.

As to the spread upward from the hilum of an active process, we may point out what occurred in influenza and bronchopneumonia.

This peribronchial thickening, however, is seen most markedly around the hilum, extending outward in "sunburst" type and rapidly diminishing in size from the hilum to about the outer one-third of the lung. The hilum becomes affected very early. There is an immediate enlargement of the hilum and a marked increase of density with irregular outline, so much so that in no case is there any doubt of the reaction of the hilum. The irregular outline is due to peribronchial thickening. In a few cases there is definite enlargement of glands at the same time in the hilum region (Honeij).

Serial radiographic examination proves, in many cases, our contention of a peribronchial tuberculosis extending from the hilum outward. These examinations show many small swellings or nodes, visible first in the hilum, then just outside, and then appearing along radiating lines into the pulmonary field. When healing takes place the original visible swellings in the hilum become denser first and those in the lung fields last. Cases that have come to autopsy show these swellings to be lymphoid tissue, peribronchial in location, and tuberculous in nature.

The question of infection by direct contact, instead of by extension along lymphatics, has been previously mentioned many times. Osler stated that "in children the enlarged bronchial glands usually surround the root of the lung and even pass deeply into the substance and the lobules are often involved by direct contact."

If we assume that the hilum enlargement in peribronchial tuberculosis is a reaction, then it must be ascertained whether we are dealing with a primary lesion in the lung or a primary infection of the lymphatics.

In conclusion then, several points are demonstrable in peribronchial tuberculosis:

1. Its relation in acute conditions to the lymph nodes in the hilum.
2. In suspected peribronchial tuberculosis the hilum is almost always enlarged and congested.
3. The process often spreads outward from the hilum.
4. The distribution of the process corresponds to the distribution of the lymphatics.
5. When the lung focus is often so small as to be barely discernible the nodes are often markedly enlarged, frequently out of all proportion to the lung lesion.

Before concluding the first part of this paper, regarding the cause, type and degree of reaction of the hilum, it may be of added interest to add the clinical picture.

Clinically, there are various opinions as to the importance of hilum tuberculosis, especially in children, and whether hilum tuberculosis can be considered an entity. Unfortunately, the frequent difficulty of diagnosing such cases exposes to a bias and results in a stupid disclaimer that such a process exists alone, or that it is frequent.

Tuberculosis of the bronchial lymph nodes, enlarged, as the cause of D'Espine's sign, is now admitted to be due to enlarged lymph nodes, not necessarily tuberculous. This diagnosis of tuberculosis of the

bronchial nodes, Bushnell says is often made from the radiograph on very slight foundation. "The fact is that pronounced swelling of the lymph nodes is characteristic of primary, not of advanced tuberculosis. It is rare that intrathoracic gland tuberculosis is of any clinical importance." Undoubtedly Bushnell asserts this opinion only in respect to the adult.

Barjon believes that "what ought to be borne in mind is the clinical and prognostic value of adenopathy which is always serious. Undoubtedly, in adults, it may sometimes indicate only a chronic and benign affection of the bronchi; but very often, in children with general poor health, adenopathy is an almost certain indication of tuberculosis." We can accept the fact that in acute diseases the lymph nodes do become markedly enlarged. Some authors believe that if these do not subside, they suggest tuberculosis, excepting of course the cases due to an otherwise known cause, such as sarcoma. Méry, d'Oelsnitz and others are firm believers in the clinical signs and symptoms of hilum adenopathy, and give a long series of cases diagnosed clinically by parasternal and paravertebral dulness, coarse breathing, modification of expiration, D'Espine's sign, tuberculin reaction, and controlled by radiographs. These authors, as well as others, lay great stress on the frail appearance of the patient, loss of weight, pallor, dry, whooping cough and thoracic changes. They believe that the disease has its starting point in the hilum, is a retrograde infection, and is of great importance.

Méry, Barjon, Fisher and others emphasize the necessity of frequent examinations in these cases for a definite diagnosis. Floyd and others declare that, from their own observations, they believe that in children in whom the bronchial lymph nodes on the right side are considerably enlarged there not infrequently occurs, at the right apex, definite signs of consolidation, such as dulness, increased resistance, limited expansion, and bronchovesicular breathing. This same fact I stated many years previously in my article on *The Importance of Mediastinal Glands*. In my conclusions I state that "enlarged glands may cause the signs which are often considered as those of early apical tuberculosis."

D'Espine states also that "an uncomplicated glandular lesion may simulate disease of the apex." The frequency of adenopathy is greater, he thinks, than postmortems indicate.

These findings are clearly related to Kronig's reports on *Collaps induratie* of the right apex, in which the symptoms closely resemble those of early infiltration. Bing also emphasizes the difference between early

tuberculosis of the right apex and the enlargement of thoracic lymph nodes.

Turban states that "displacement of the heart dulness three-quarters of an inch or more to the right, with or without displacement of the heart, is such a frequent symptom of moderate contraction at the right apex, that I consider it a typical and cardinal symptom of right apical disease of some standing." It is not unlikely that the frequency of this finding may be due to hilum enlargement and that Turban's explanation is erroneous; anyhow, it applies to the diagnosis of early right apical disease.

The form of hilum tuberculosis which Eliasberg describes is in infants, with the much discussed apical changes. He gives a case of an infant seven months old.

Barlow and Thompson state that

> the conclusion is inevitable that in the course of apical tuberculous infection the definite apical lesion is frequently preceded by much smaller parenchymatous lesions in the region of the hilum, which extend to the pleural surfaces and are similar in every respect in size to the early lesions of manifest tuberculosis; and it is equally obvious that the incipient apical lesions may not always represent all of the tuberculosis from which the man is suffering, but that there may be peribronchial, glandular and parenchymatous lesions at the hilum which in their aggregate exceed the apical lesion itself.

The swelling of the lymph nodes, furthermore, can be observed symptomatically only when it produces a mechanical obstacle (Pirquet). This writer also states that tuberculosis of the hilum nodes leads in small children frequently to chronic dyspnoea. In the radiogram we then find the enlarged bronchial nodes, and the tuberculin reaction elicits their tuberculous nature.

In youth, Philippi says, there is seldom a true hilum process without more or less disease of the hilum tissue, in the form of a peribronchitis and infiltrative process of the adjoining pulmonary parenchyma, which can be diagnosed both clinically and by radiographic examination.

Cooke and Hempelmann, reporting on a series of 131 cases under 15 years of age, state that they found paravertebral dulness present in four-fifths and D'Espine's sign in four-fifths of the cases. Practically all the cases showed hilum changes and often hilum shadows on the radiograms extending well into the lung. There was a uniform agreement between the size and position of the hilum shadows and the paravertebral dulness. The Pirquet test was positive.

Wessler believes the disease to be an entity and that it occurs mostly on the right side, agreeing with many authors and with my own findings. The form he describes is similar to that described by Méry, et al, Barjon and others. In Wessler's cases the physical examination was mostly negative. There was, however, loss of weight, general debility, etc.

In Heise and Sampson's comparative classification, by physical signs with roentgen ray control, several points made have a bearing here. Sixty-eight per cent of the cases reported by them showed a definite peribronchial lesion, when the physical signs were doubtful or negative. In 78 incipient cases, 42 per cent gave peribronchial evidence and of 120 moderately advanced and far advanced cases only 8 per cent gave peribronchial lesions. These figures are given here merely to show the importance of an early recognition of peribronchial changes and, as has been pointed out, these changes are definitely related to the hilum changes.

In concluding the clinical resumé of the question, we have to bear in mind that too great an emphasis should not be laid on such discernible changes in the paravertebral or parasternal areas as given in suspected cases, as such cases frequently do not give radiographic proof of hilum lymph nodes.

I still believe that D'Espine's sign is of value in the examination of children. Disappointments do occur constantly in one's ability to diagnose these lymph nodes; but much less seldom are they missed, when present in marked cases, than diagnosed as being present when radiographic evidence shows a clear thorax.

THE POSITION AND GENERAL APPEARANCE OF THE HILUM

The hilum area considered here is formed by the root of the lungs, the arteries, veins, lymphatics, pleura and lymph nodes immediately surrounding it. It includes at times the space between the right and left lung roots, the mediastinum proper. It extends outward, laterally, upward and downward to approximately the fourth division of bronchi (Barjon), commonly designated as between the 2nd and 4th ribs. Physically, it is an indefinite area, more easily defined in children when pathological changes are present than in adults under the same conditions. Roentgenologically, the area is more easily defined and fits more or less the above description. Barjon, in discussing diseases of the pleurae, defines the hilum area as follows: "Anatomically the region

of the hilum is one of the most complex parts of the pleura. In the hilum is a sort of open space, found at the junction of all the secondary diverticula of the pleura. The large pleural cavity, the interlobes, the anterior and posterior spaces of the mediastinal pleura, all end in the neighborhood of the hilum." As we are concerned mostly with adenopathy of the hilum area, we have to consider the anatomic distribution of lymph nodes of this region. Barjon, apparently influenced by Baréty's classification, gives two main groups of lymph nodes:

1. A mediastinal group, including all tracheobronchial nodes, that is, the two pretracheobronchial groupings, right and left, and the intertracheobronchial grouping. All these are situated in the median line between the sternum and the vertebral column, in relation to all the important organs of the mediastinum.

2. A hilum or pulmonary group, made up of many intrapulmonary peribronchial nodes, which follow the bronchi subdivided up to the fourth division (Cruveilhier). These have a lateral location.

A study of the diagram from Sukiennikow's work shows the greater number of lymph nodes to be on the right and along the main bronchial vessels; there is also greater massing of nodes on the right, as well as chain formation. Sukiennikow, describing the development of the tracheobronchial and the bronchopulmonary lymph nodes, concludes that the appearance and the grouping of these nodes have a fixed regularity of massing and that those situated in the angle of the bronchi are bound there. Sukiennikow states also that the prevailing position of the lymph nodes is anterolateral, especially the tracheobronchial group, and gives this as a reason for the difficulty in diagnosing them, when enlarged, by percussion.

Baréty, in his six illustrations, shows very well the wide distribution of these nodes and their enlargement and form.

Miller, investigating the lymphatics and lymphoid tissue of the lung, reports that along the larger divisions of the bronchial tree, true lymph nodes have been described by a number of investigators. In each instance they were found in the angle formed by the dividing bronchi.

ROENTGENOGRAPHIC EXAMINATION OF THE HILUM

The shadow of the hilum deserves also special study, says Barjon. When it is normal, it does not signify that the pleuropulmonary tissues are intact; but when it is abnormal (more extensive and denser) there most often exists a pleuropulmonary reaction requiring investigation.

Adenopathy of the hilum group is much more directly related to the condition of the lung, particularly to the development of pulmonary tuberculosis, as Piéry and Jacques have well shown, but it may also precede pulmonary lesions (Barjon).

The shadow of the hilum, as usually seen, is somewhat crescent-shaped and elongated, commonly 2 or 3 cm. wide at its centre and gradually thinning out at the two extremities. It is situated at the edge of the median shadow and separated from it by a narrow band of semitransparency. The convex side of the crescent is toward the median shadow. The upper extremity is shorter than the lower; the lower projects into the lower one-third of the pulmonary field. On the left the hilum is hardly ever seen as clearly as on the right, and quite commonly is not seen at all in an ordinary roentgenogram. The ends are ragged in outline and the inner border usually more clearly outlined than other portions. When there is an increased density at the root of the lung, such as occurs in bronchopneumonia or in tuberculous pneumonia of children, then the more distinctive features of the hilum, as described above, are obscured. In tuberculous patients the shadow of the hilum is very often modified in an early stage; this, we can be assured, occurs more often in children.

Tuberculosis of the hilum, not necessarily lymphglandular, may precede pulmonary tuberculosis. This mode of onset has been admitted by many clinicians, as has been stated previously, to occur quite commonly in children (Rieder and Rosenthal, Méry and his collaborators, Wessler, Much, von Ohlen, Greenberg).

Many conditions may produce changes in the form, size and density of the hilum. These numerous changes cause difficulties of diagnosis in many cases, and give rise to contradictory statements by many observers, partly because of lack of experience, pathological training or incomplete methods of examination.

Conditions in the lung, transitory or acute, adjacent to the hilum, bronchial or peribronchial inflammation, circulatory, pleural lymphatic and gland conditions may produce changes directly. Conditions in the organs of the mediastinal area may produce changes in or of the hilum indirectly.

"In active destructive disease there is a hilum that is widened, accentuated, mottled or broken, often studded with puffy, bulging nodules (presumably tubercles or hypertrophied lymph nodes) and usually of an indefinite, hazy or fuzzy outline. The latter is sometimes indiscernible." (Amberson.)

The hilum reaction in children differs considerably from reactions in adults. The changes in the adult are more difficult of interpretation and prognosis most often impossible.

Much quotes Kantz who says, "Gradually the demand for roentgen examination in pulmonary tuberculosis of the adult has become more and more general. But of still greater necessity and importance is the X-ray in pulmonary tuberculosis of children. We know, he says, that in about 90 per cent of the cases of childhood the tuberculous focus is located in the glands of the hilum." Also, "in childhood the differentiation of a normal hilum shadow from that of a tuberculous one is sometimes impossible, even if anthracotic or other indurations of the hilum glands, due to inhalation of dust, are extremely rare occurrences."

Engel, whom Floyd also quotes, states that "the change in the position of the gland and bronchial shadows (hilum) with increasing years is noted; in the child they bordered on the heart shadow, and in adult life tend to fuse with the central heart shadow."

The difficulty of interpretation of hilum reactions in the adult is furthermore seen in so called miners' phthisis, in which tuberculosis is superimposed on a silicosis (Irvine and Watt).

Hilum changes embody a dependable index of the degree of progression or retrogression of the adjacent disease, and are subject to prognostic and pathological interpretations which no pulmonary roentgenologist can afford to ignore (Amberson). This same opinion I expressed in an article on the importance of adenopathy in reference to pulmonary tuberculosis.

"Skiagraphic study of the chest resolves itself into two natural divisions; one pertains to the hilum regions, concerning especially the bronchial glands with their associated peripheral lymphatic nodes, and the other includes the parenchyma of the lungs itself." (Sewall and Childs.) These writers also state that the hilum presents one of the most characteristic and important skiagraphic features of the chest.

"Bronchial gland tuberculosis is more difficult to interpret on account of the normal existence of a pronounced hilum shadow and the frequent occurrence of nontuberculous enlargements of the hilum glands by anthracosis, etc." (Potter.)

Engel states, however, that tuberculous bronchial lymph nodes give such a typical roentgen picture as to be good enough to be without question, but he adds that a definite diagnosis can only be made in a few cases.

One of the difficulties of interpretation of hilum shadows is to determine when the process in the hilum is no longer a true hilum process and when it has become a pulmonary parenchymal process.

Pleural reactions also, over the hilum, extending in any direction, especially upward (vertebral) and outward (interlobar), may be mistaken and interpreted as hilum reactions.

The writer agrees with Potter in the first part when he says that "increased hilum shadows have more diagnostic importance in children than in adults and are especially important if asssociated with definite pulmonary infiltrations at a distance from the hilum."

In most cases, Krause states, apical findings are wanting; therefore, he emphasizes the value of shadow variations at the hilum as being all the more important.

Méry, *et al.*, describe three forms of shadow of the hilum in their article on adenopathy:

(1) Triangular, with base of triangle at hilum, apex outward.

(2) Vertical elongated, from hilum to apex.

(3) Transverse band, occupying upper lobe from interlobar fissure.

The third type conflicts with a diagnosis of interlobar pleurisy and concerns circulatory congestion, from which they have to be differentiated. Sluka also described three similar forms. These three types represent activity of the hilum nodes, a great many cases of which have occurred since the influenza epidemic. In my opinion, however, they are all well developed types which are comparatively easy of diagnosis. All three types may give parasternal dulness on physical examination.

Rieder states that when tuberculosis in children becomes localized in the bronchial lymph nodes, line shadows extending from the hilum indicate a peribronchial lymph infection with tubercular infiltration. He gives a classification of three forms:

(1) An isolated infection of bronchial and mediastinal lymph nodes, that is, hilum tuberculosis.

(2) A combination of hilum and apical disease, or hilum and upper, middle or lower lobes, and

(3) A disseminated tuberculosis.

Recently I was fortunate in having Dr. J. H. Green of the Monroe County Tuberculosis Sanatorium, New York, send me some beautiful radiographs of cases which correspond very closely to these types,—a portion of the excellent work which he is undertaking.

Méry and Girard present a frequent and latent type of tracheobronchial adenopathy. Believing it to be an intermediate stage between childhood tuberculosis and adult tuberculosis, they think it a lymphatic process. The two forms which are presented are (1) mediastinal adenopathy, which is developed at the expense of the anterior or intertracheal-bronchial lymph nodes or (2) a hilum adenopathy involving the interbronchial node group, which occupies the hilum area. Three other interesting forms of tuberculosis are also given: a periadenitis form which gives rise to pleurisy and parenchymal infection, a periglandular congestion form which gives greater symptoms and signs posteriorly, rather better than anteriorly, and a pleural periadenitic interlobitis which Méry states is due to a bacillemia and is an elective infection by retrogressive lymphatic involvement from the hilum. To my mind these divisions complicate rather than clarify the question of tuberculosis of the hilum. Undoubtedly analogous types can be determined, but only by studying the individual case over a long period of time. This does not help us in the earlier and more important period of diagnosis. It also appears to me as being a pathological rather than a roentgenological diagnosis.

Ranke divides the course of chronic generalized tuberculosis into three classes: (1) a latent stage, (2) a primary manifestation stage with regional lymph node affection; and (3) a metastatic stage.

The second stage interests us; this is recognized by the affection of bronchial pulmonary lymph nodes. As the process advances the lymph node affection becomes more pronounced; the more chronic the course, the more evident the nodes. An understanding of this form is had by comprehending Miller's article on the lymphatics and lymphoid tissue of the lung and their relation to disease processes.

In relation to the same question Dufort makes an interesting statement in a study of the treatment of mediastinal adenopathy by heliotherapy. He states that from 40 to 50 per cent of cases of simple adenopathy respond to treatment, but this does not include cases in which there are pulmonary lesions. In these cases there is a tendency for diffusion of the process.

v. Ohlen, in studying the early diagnosis of hilum lymph node tuberculosis, stated that in all his cases in which the tuberculin test was positive certain hilum changes were observed roentgenologically and that the intensity of the reaction was parallel to the hilum changes.

The question in this particular is whether these changes indicate an early hilum node tuberculosis, perhaps at its onset.

v. Ohlen stated further that when the roentgenogram shows a sharply glandular focus, confirmation of hilum node tuberculosis is assured, and when it shows changes of a more general nature, as in the majority of v. Ohlen's cases, it is a strongly supporting factor. However, v. Ohlen states that only in a few cases are the roentgen signs positive proof of hilum tuberculosis. He advocates repeated examinations, as does Méry, Barjon, Rominger and others, as giving valuable information on the regression and progression of hilum processes.

However, the point to emphasize is not only the value of repeated examinations but the added fact that a diagnosis of hilum tuberculosis should be based on the association with clinical symptoms and physical findings.

Scherer also draws attention to the difficulty of differentiation between a normal hilum and early disease under certain conditions. Difficulties may be caused by vessels being superimposed, or by distortion, congestion and so forth.

Assmann believes that mitral failure and congenital cardiac failure, through dilatation of the arteries, cause an increased hilum shadow.

Personally, I believe that any congestion of the pulmonary vessels, especially if associated with coughing, produces an increased density of the hilum shadow.

In an excellent paper by Méry, Détré and Desmoulins, on the clinical and radiological diagnosis of glandular pulmonary tuberculosis in children, a thorough presentation is made of the value of clinical signs and symptoms and radiological appearances of hilum lymph node tuberculosis. They point to the value of the family history and the patient's personal antecedents. The authors believe that a diagnosis of hilum node tuberculosis can be made by clinical methods controlled by the X-rays and tuberculin test.

The progressive changes in the hilum are described as follows:

First: slight extensive stage (the right base most), with the "web-foot" appearance of the shadows, appearance of nodules of the same density. Commonly seen in children after certain diseases.

Second: hilum manifestations, more branches and softer (as shadows); the appearance of a "butterfly wing." It may be unilateral and may border on the mediastinum; the external contours are variable: the interlobar pleural reaction is frequent: the "crowding together" of the shadow.

Third: the hilum shadows become clear again and distinct; the ramifications darker with small calcifications; the shadows are more extensive with pleural adhesions.

The description of the third stage evidently has to do with a healing process or may apply in some cases to a general low-grade pulmonary process.

These stages Méry, *et al.*, point out have been corroborated by autopsy findings.

The three questions which arise in an examination of this sort are the following, according to these authors:

First: At what point in their development has the process arrived?

Second: What is the degree of activity?

Third: What is the menace?

Barjon divides tracheobronchial adenopathy into two main groups on account of their different medical significance:

(1) *Mediastinal:* found after measles and other infectious diseases in children. In adults, in tuberculous lymphadenitis, cancer, etc. This group has no relation to pulmonary conditions.

(2) *Hilum*: this affects more directly conditions in the lungs, especially pulmonary tuberculosis (also in bronchitis, bronchiectasis, pneumonia).

The second group is easy to see and is often confused with the hilum. If the latter is unaffected, a clear space is seen (previously described) between it and the median shadow. If it is affected the shadows are fused. "But," says Barjon, "early tuberculosis of the glands of the hilum, with caseation and without a pulmonary lesion, is not uncommon."

It is difficult to impress the fact that the hilum presents different types of density and form, and that not merely an enlarged or dense hilum is a warrant for diagnosing tuberculosis of the hilum. Recently, a pulmonary-disease specialist stated that the hilum reaction was upon examination a mere fallacy.

Dunham also states, "in the past the roentgen diagnosis of pulmonary tuberculosis has rested upon changes of density in the hilum and the heavy trunks,—I wish to show you that the earlier changes take place in the linear markings. And further I wish to show you that these changes are due to tubercles scattered along the finer branches of the bronchial tree." However, Dunham bases his opinion on patients who were twelve years of age or more. The pathological changes of tuberculosis and of the hilum commence at a much earlier age. Dunham may

have in mind a second stage of lymphatic peribronchial tuberculosis, miliary tuberculosis or forms of adult tuberculosis, but which in no case concerns hilum tuberculosis of children.

Floyd, quoting Heubner, states that the picture of the diseases of the tracheobronchial lymph nodes is entirely a problematical sketch, and, as he thinks, a correct one. The extreme point of view may be seen in the statements of Ochsner, who says "that the X-ray gives no positive evidence in nearly 50 per cent of the cases, that it gives less positive evidence than the tuberculin test and that the X-ray is of no value, except in a negative sense, until extensive pathological changes have taken place, this occurring in most cases long after the symptomatology and physical examination are well marked." "Furthermore," says Ochsner, "enlarged root glands are not considered positive, as they have been found in nearly all cases examined."

In association with hilum disease is the pleural reaction frequently observed in acute disease and especially in children. In tuberculosis it is a common reaction and frequently the means through which a definite diagnosis of tuberculosis is reached. The reaction of the hilum, that is, an acute inflammation of the lymph nodes with surrounding congestion or periglandular inflammation with very little general congestion has, as part of its reaction, frequently, a pneumonia or a pleurisy or both.

Méry, *et al.*, lay particular stress on the interlobar pleural reaction and this point is well taken up by Paillet in his excellent monograph. Barjon, as also Piéry, emphasizes the importance of the interlobar reaction. These authors agree that pleurisy is an added indication of active hilum adenopathy. Riviere believes that pleurisy is a very frequent complication of hilum tuberculosis. Adami and McCrae showed, in 11 cases out of 93, the relation of pleural adhesions to healed and latent tuberculosis. In these 11 cases tuberculosis existed in the thoracic nodes and 6 in combination with disease of the lungs. Baréty described fully these adhesions resulting from glandular and periglandular inflammation and also their sequellae. Finally, Miller again gives us our basis for consideration of this subject, for, as has been stated before, he has pointed out the relation of the lymphatics to the pleura.

It is left to Powell and Hartley, however, to stabilize excessive enthusiasm on the part of students of this question, as they say, "in a great majority of patients in whom the symptoms and signs suggested an early lesion of the lung we have derived no assistance whatever from the X-rays, the appearance being always negative—further, in certain

patients in whose sputum tubercle bacilli were present, proving that the lesion was no longer an early one and in whom definite physical signs were observed, the X-ray examination still showed no abnormality."

THE HEALING SIGNS IN THE HILUM SHADOW

By bearing in mind the description of the hilum when acutely affected, following any of the acute infectious diseases or tuberculosis, we shall be assisted materially in interpreting signs of healing.

It may be well, however, to quote again and present Méry and Détré's description, "the hilum ramifications are more intricate and more soft; it appears as if a smudging of the shadows had occurred. The sheath which crowds together these shadows fuses with the mediastinum; this lacework of shadows appears faintly clear on both sides of the median shadow like the wings of a butterfly." We can say further that the hilum area is enlarged, its density is increased, the shadows being very "soft" in appearance, and that the hilum appears "swollen."

In healing there first take place changes in the above description. The hilum becomes gradually less soft and the ramifications more distinct and the shadows harder. Méry speaks of fragmentation of the shadows. Spots or small hard shadows are discernible through the hilum shadow. The hilum may become more clearly defined and smaller.

Regressive changes in the hilum region in children do not necessarily indicate healing. These changes can only be determined over a long period of time. The regressive changes from a tuberculous pneumonia, for instance, or from acute enlargement of lymph nodes with congestion, can be so reported, but regressive changes in tuberculosis of the hilum area must be dealt with most conservatively.

Amberson presents two illustrations which indicate well what has been attempted in words. In one figure (on page 37) "the hilum is accentuated, widened, and the outline is indefinite and fuzzy. In figure 2 it is sharply outlined, stands out in contrast to other parts of the field and has something of its normal contour. Such a hilum transformation invariably signifies reparative changes in the adjacent lesion, provided there are no complicating factors."

"It is difficult to ascertain enlarged and changed bronchial glands roentgenologically except where they are enlarged and lime salts have been deposited. If they are not thick and enlarged, to be recognized they must be homogeneous, corresponding in size and contour and con-

forming to the projection of the bronchial tree" (Engel). This opinion applies in part to what is seen in the healing stages and is in no way of diagnostic value in the acute stages.

We might go a step further if we could agree with Engel, and agree with Dunn and Cohen, who state that "the primary lesion of the lung is usually not shown in the roentgenograms; it is too small," or perhaps with the second part of their opinion that—"or if the roentgenogram of the chest shows the shadow characteristic of tracheobronchial *lymph node* enlargement, a diagnosis of primary tuberculosis in the lung may be made with a fair degree of certainty."

Barjon states that "all that is necessary to bear in mind is that the presence of deeper and more defined shadows in the midst of homogeneous hilum bands corresponds to sclerous or calcareous glands, denser than simple hypertrophied or caseous glands."

Méry and collaborators describe the third stage as a stage of healing when the hilum shadows become again clear and distinct, and the ramifications darker with small calcifications. The shadows are more extensive and pleural adhesions may be present.

A sensible precaution was taken by the Surgeon General against interpreting these denser shadows as significant of tuberculosis. "The presence of masses in the neighborhood of the hilum as shown by the X-ray may indeed be cause for rejection, but rejection on account of relatively small opacities in that region on the ground that they indicate a bronchial gland tuberculosis of clinical importance certainly should not be permitted."

If healing does take place the signs appear more rapidly and more definitely in children and young adults. Interpretation of changes in the adult in suspected cases is exceedingly difficult. A study of the lung changes in all cases of pulmonary tuberculosis coming to post-mortem, that have been previously radiographed, is of extreme value.

If healing does not take place, then involvement of the lung, interlobar pleura or both, does take place. The most important change and form of infection is the hilum pneumonia tuberculosis, frequently seen in the very young and so well described by Méry, Barjon and others, a problem on which Green is working. The consideration of this question concerns pulmonary changes with which we are not directly concerned.

In conclusion, the question that is quite predominant in considering hilum tuberculosis in the adult is that made by Rist and others: what

becomes of the bronchial tuberculous lymph nodes of children who recover? The appearance of calcified nodes in the adult is frequent and others, by their density and appearance, suggest fibrosis. These changes are of little value in the adult when unassociated with other changes; but I am convinced that calcification occurring in the young adult is of significance. It is a sign of healing, and logically can be nothing but an indication of a preceding tuberculosis of the lymph nodes.

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THE BLOOD LIPASE IN PULMONARY TUBERCULOSIS[1]

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The forces which bring about chemical reactions, constantly taking place in every cell, are supposed to reside in the enzymes, whether excreted by the cell or existing within it. Thus, "we may look upon the intracellular enzymes as the most important known agents of cell metabolism and, consequently, of all life manifestations, and the changes they undergo or produce in pathological conditions must be fully as fundamentally important as their relation to physiological processes." The true nature of enzymes is not at present thoroughly understood, but the weight of evidence is in favor of the view that they are specific colloidal substances, although perhaps differing widely in chemical nature. Enzymes have been shown to be specific, lipase affecting only fats and trypsin only proteins; and the fact that, when injected into animals, they give rise to the formation of specific immune bodies is further evidence of their material existence. It has also been shown that enzyme action is in no way different from chemical action observed independently. The fundamental consideration is that chemical reactions are reversible, that is, their tendency is to establish an equilibrium and the change may be from either side of the equation. Enzymes act like catalytic agents, increasing the speed of reaction. They therefore merely hasten reactions which would go on without them, although very slowly, and they do not initiate or change the nature of the chemical reactions at all. The reversible nature of the enzyme action explains many problems of metabolism. All enzymes are most active between 35° and 45°C. Although they can stand a temperature of 100°C. or more when dry, in water they are usually destroyed somewhere below 70°C. Low temperature, even —190°C. (liquid air) does not destroy them. This very brief description of enzymes is drawn largely from Wells's *Chemical Pathology* (1).

Of recent years attention had been called by many investigators to the supposed rôle played by the serum and cellular lipase in the destruction of the tubercle bacillus in tuberculosis. The basis of this belief

[1] From the Loomis Sanatorium, Loomis, New York.

rests chiefly on the fact that, because the tubercle bacillus is rich in fat, it would require the action of some form of lipase for its destruction and digestion in the host. Most interesting observations have been made, either along these lines or at variance with them. Bergel (2) found that fat and lipoids have an elective chemotactic effect on the lymphocytes; so that, following the intraperitoneal injection of such substances, the latter, and not the polymorphonuclear leucocytes, wander out of the blood vessels and engulf and digest the fat by virtue of their lipolytic power. Among the lymphocytes he includes the transitional and the large mononuclear forms which, although they have irregular and indented nuclei, are never polynuclear and never have a basophilic protoplasm. But his most interesting observation had to do with the fate of tubercle bacilli in a resistant animal. He reports that, if a white mouse is injected intraperitoneally with tubercle bacilli, in the characteristic exudate which forms the bacilli will be taken up to a small extent by the polymorphonuclears, but mostly by the lymphocytes, the latter being in excess. The degree of absorption and digestion can be followed by noting how the bacilli in the cells lose their ability to stain with fuchsin. As a final stage, the red pigment is seen free in the lymphocytes and, when this disappears, the fat is considered completely digested. The remainder of the bacillus is now no longer demonstrable by Ziehl's method, but its persistence in granular form can be demonstrated by Much's stain. These so called Much's granules, therefore, are not special forms of tubercle bacilli, but are a result of the breaking down of the fat of the tubercle bacillus in the process of destruction. The bacilli are now no longer acid-fast, but stain blue with Ziehl's stain. If a second intraperitoneal injection of the same bacillus is given, the bacilli are phagocyted and defatted more rapidly by the lymphocytes, so that it would now seem that the lipase of the lymphocytes is more active against the bacillus, particularly as its action is now extracellular as well as intracellular. The author does not state definitely whether the lipase in question is specific, but points out that it can be specifically increased for tubercle bacillus fat. In guinea pigs the reaction is similar but not so pronounced as in mice. Bergel believes that in tuberculous tissues the antibodies, at least as far as the fatty parts of the bacilli are concerned, originate from the surrounding wall of lymphocytes, and he concludes that the lymphocytes are the natural weapons against tuberculosis: they are the biological reagents against fatty substances. He draws a similar analogy with syphilis. In this disease he believes that the causative agents, the

spirochetes, which are fairly rich in lipoids, are destroyed by a fat-splitting ferment derived from the lymphocytes. Thus, the reaction of syphilis (primary or later) consists in an accumulation of lymphocytes and the action of their derivatives (lipase). With the swelling of the lymph nodes, the blood lipase is found to be increased.

Jobling and Petersen (3) have elaborated a theory concerning the origin of caseation in tuberculosis. They believe that, due to the presence of the soaps of the unsaturated fatty acids derived from tubercle bacilli, the cells destroyed by the action of the toxin are not removed by autolysis, as these soaps are active agents in preventing this. The anemia caused by the occlusion of the blood vessels plays an important part, as the lack of fluid prevents the dilution and subsequent absorption of the inhibiting substances. Hence, the caseous area gradually increases in size as the bacilli invade and cause the death of the surrounding tissues. This theory is *absolutely* dependent on the presence of a lipase which hydrolyzes the neutral tubercle bacillus fat, and the acids are then saponified. Jobling and Petersen do not mention the source of the lipase, except to refer to Bergel's statement that it is present in the lymphoid cells of tubercles and to the fact that Corper found lipase in tubercle bacilli.

Kollert and Frisch (4), on the other hand, deny Bergel's theory of the close connection between lipase and lymphocytes. They point out that the mononuclear elements in many exudates are not lymphocytes, but the broken-off and possibly converted endothelial cells of the serous membranes. As a matter of fact they found the lipase (butyrase) value in tuberculous exudates to be only about one-half that of the blood serum. The question whether the tubercle bacilli are destroyed by the mononuclear cells of the body is very easy to answer, but it is hard to say what kind of cells they are and wherein their power lies. Also, the idea of humoral allergy against tubercle fat is not tenable. They admit that there appear to be present in the human blood substances which destroy tubercle bacilli, but what connection serum lipase has with these is at present very uncertain. However, it would seem that as the bacillus loses its fatty envelope it loses its virulence. Whether lipase gives resistance to the individual against infection is yet to be determined. Their investigations lead Kollert and Frisch to conclude that there is no relation between the lipase content of the blood and the lymphocyte count.

Recently Foot (5) has very definitely shown that the large mononuclears, which are the cells chiefly concerned in the discrete foci of tubercu-

losis, have a special origin from the vascular endothelium and possess a special functional capacity for ingesting solid foreign particles. He believes this function is not possessed by cells derived from lymphoid tissue.

In a study of the relationship between lipin-protein and acid-fastness Long (6) pointed out that, although the loss of acid-fastness of the infective agent may mean the successful action of a destructive agent which has penetrated the waxy barrier, there is lack of precision in the idea that such penetration and disruption of the cell body means lipolysis. He believes that it is more reasonable to suppose that what has been accomplished is not a splitting or solution of the wax itself but a separation of it from its protein combination. Lipases and esterases are not concerned in this action, and, if it is accomplished, the action of lipases and esterases may well be dispensed with. To support this belief he mentions how difficult it is to imagine weak enzymes in watery solution attacking vigorously and successfully tubercle bacillus wax which ordinarily can be boiled for five hours with 25 per cent potassium hydroxide without being split.

During the past year, at the Loomis Sanatorium, we have made an attempt to estimate the lipase (*esterase*) activity of the blood serum of many of our patients. This was done chiefly on admission, and largely with the idea and hope that such findings might be of value in estimating the resistance of the individual patient, particularly if the blood lipase is specifically affected in tuberculosis and is really a factor in the destruction of the tubercle bacillus. Prognosis in tuberculosis is always difficult, and any test or procedure lending aid to it would be of definite worth. In a few cases later estimations were made, but the bulk of our findings have to do with the admission or first estimation.

A partial review of the literature revealed the fact that the quantitative study of lipase activity through the cleavage of the higher fats is very technical and difficult. Hanriot (7) in 1896 claimed to have been able to bring about the hydrolysis of oils and natural fats with serum ferment. This claim has been denied by most investigators. The technical difficulties in dealing with fats and higher fatty acids led to the introduction of simple esters in the investigations of the action of fat-splitting enzymes, as these lower fats are more readily hydrolyzed by such enzymes. Practically all the work so far reported as to the occurrence of lipase in blood and tissues has been done with these esters. In 1893 Berthelot (9) introduced the use of monobutyrin, a simple ester

of butyric acid. Kastle and Loevenhart (8) were the first to use ethyl butyrate as an artificial substrate. This ester had the great advantage of being in the market and readily obtainable in pure condition. Tributyrin, salicylic acid esters and glycerol triacetate have also been generally used. It must be borne in mind that these esters are artificial fats and do not occur in nature. Hence, in evaluating all reported findings, the question naturally arises whether the enzyme found present is identical with the true fat-splitting ferment, the lipase, upon the action of which our modern conception of fat metabolism depends. Are these substances (ferments), which so readily attack and split the artificial esters, but which are apparently inert against the natural fat of the body, really true lipases at all? Are they similar in character to the lipolytic enzyme of the pancreatic juice, which under suitable conditions has the power of splitting neutral fat into fatty acid and glycerine?

In 1900 Kastle and Loevenhart effected the synthesis of ethyl butyrate from ethyl alcohol and butyric acid with pancreatic lipase, showing that the reaction is a reversible one. Several investigators have confirmed these results. Loevenhart (8) believes that the work on ethyl butyrate is directly applicable to the natural fats. He argues that there can be no doubt that the hydrolysis of monobutyrin and ethyl butyrate by serum and extracts of most living tissues must be included in the group of reactions called fermentative or enzymic, and the only thing which is open to question is whether we are to attribute the hydrolysis of the esters of the lower fatty acids and the fats to one and the same enzyme or to different enzymes. The fats and the esters of the lower fatty acids are hydrolyzed and synthesized by the same chemical methods and are absolutely analogous from a chemical point of view. It is true that they differ widely in their physical properties, but are these of such character as to necessitate entirely different enzymes in these processes? If we assume this, the question naturally arises whether the hydrolysis of each ester would not have to be regarded as a distinct activity and attributed to a distinct enzyme. Von Hess (10) also believes that the ester-splitting enzymes are true lipases and that their action is, qualitatively, directly applicable to the hydrolysis of natural fats. However, Arthus (11), Doyen and Morel (11) and others claim that the blood serum does not contain a true lipase, but only esterases of the lower fatty acids. They admit that the artificial esters and the higher fats are analogous from a chemical point of view, but point out that the experimental facts show conclusively that the serum enzymes only hydrolyze the simple esters and this may

have no relation to the capacity of the serum to split natural fats. In part, this is the view of Wells (12).

From the above it can be readily seen that the question of the identity of these ester-splitting ferments with true lipase is not at all settled; hence, careful investigators refer to these enzymes as *esterases* or *butyrases* to avoid criticism. In this article, for convenience, we shall continue to refer to these ferments as *lipases*, because the fat-splitting enzymes are generally known as such and we are much more familiar with this term. But this is done with the full realization of the above mentioned strictures.

METHODS AND FINDINGS OF OTHERS

The usual method for detecting and estimating these so called lipases has been to incubate a given amount of the serum or tissue extract to be tested with a solution of one of the esters, and then to estimate the amount of hydrolysis (acid formed). The reaction which takes place, using ethyl butyrate as an example, may be expressed by the following equation:

Ethyl butyrate *Alcohol* *Butyric acid*

$$C_2H_5- O - OC - C_3H_7 + H_2O \rightleftarrows C_2H_5 OH + HOOC - C_3H_7$$

Water must be present in excess to bring about the maximum hydrolysis. Although the equation is written as though it were a reversible reaction, it is likely that very little reversion takes place in the presence of an excess of water. The *lipase* merely acts as a catalyzer, and increases the speed of the reaction, which would require a very long time without this agent. As soon as the concentration of acid formed reaches a certain point, the action of the lipase is inhibited. The lipolytic activity of the substance tested is generally reported in terms of the acid produced, which is usually determined by ordinary titration methods. An improved method has been devised by Rona and Michaelis (13) for testing lipase activity. They estimate the amount of hydrolysis by measuring the change in surface tension instead of by direct titration.

A considerable number of investigators have studied the lipase content of the blood both in health and disease. Among the earliest of these are Achard and Clerc (14), who found the lipase (butyrase) activity to be lessened in most diseases, and increased and decreased with the health of the patient. Sagal (15) studied 110 blood sera of which 16 were from normal individuals. He found that in hepatic cirrhosis and in carcinoma the lipase is much reduced. With syphilis, and bacterial diseases in general, there is a slight increase in lipase activity. In nonbacterial diseases, conditions of increased growth energy (pregnancy), cardiovascular disease and nephritis, the enzyme is chiefly diminished. Sagal showed that the activity of normal sera is fairly

constant and that the maximum of enzyme activity, independent of diseased conditions, occurs in young persons, with a slightly diminishing value for each succeeding decade. Whipple and others (16) also reported the lipase (butyrase) to be fairly constant in normal human beings and animals. They found that injury to the liver, by chloroform or phosphorous poisoning, always causes a rise in the plasma lipase. In eclampsia, with hemorrhagic necrosis of the liver, the lipase is also high. Chronic jaundice may show low lipase. All acute infections show a normal lipase except those in which the intoxication has caused more or less liver necrosis, focal or diffuse. Bauer (17) in 1912 made a careful study of the blood lipase (esterase) in carcinoma and tuberculosis, using the method of Rona and Michaelis. Many tests on the same subjects gave constant values. Bauer found the lipase content reduced in carcinoma and far advanced phthisis, usually markedly so. Cases of phthisis, about to die, often give a constant of from only one-half to one-fifth that of normal serum. On the contrary, in early and benign tuberculosis an increase of lipase was found. Kollert and Frisch (4) reported similar results. They found the fat-splitting ferment to be high in fibrotic tuberculosis and low in caseous and exudative types. They also investigated the lipase value of tuberculous exudates and found this to average only one-half of the blood-lipase value. They concluded that lipase determination at regular intervals on tuberculous patients shows a fluctuation of value which approximately runs parallel to the condition of the patient during the period of observation. Levinson and Petersen (18) have recently investigated lipolytic (butyrase) activity in pulmonary tuberculosis. They found that normally the serum lipase index is between 15 and 16, in the incipient cases 10 and 12, moderately advanced 6 and 8, and in the far advanced 3 and 4.

TECHNIQUE (GENERAL)

The method of Rona and Michaelis is apparently the most accurate of all techniques. They have shown that the velocity of the hydrolysis of tributyrin solution is approximately proportional to the amount of ferment present and that the product of the hydrolysis, if an acid reaction be prevented or neutralized, has no influence on the velocity of the reaction. So the velocity constant at various times must remain practically the same. Usually three determinations of the surface tension of the mixture of tributyrin and serum are made after 30, 60 and 90 minutes. This is done by means of the stalagmometer, the tubes in the meanwhile being kept at constant temperature, usually from 18° to 24°C. By comparing these findings with the surface tension of the water and the tributyrin solution, a constant is worked out, which accurately represents the amount of hydrolysis of the ester that has taken place. Falkenheim and Gottlieb (19), for clinical usage, recommend a modification of this

test, in which the time for the saturated tributyrin solution to be 50 per cent disintegrated is taken as the index of lipolytic activity, instead of the usual constant. Hence, the weaker sera will take longer than the stronger.

THE TECHNIQUE USED

As it was necessary for us to do this work in conjunction with our routine blood-tests, in which many sera were examined at a time, the surface tension method seemed impracticable. It is costly, and tributyrin is not easily obtained. Hence, we were compelled to turn to the more simple, if less exact, procedure of direct titration of the acid formed by the action of the blood ferment on some suitable ester. Ethyl butyrate is commonly used for this purpose, and the "concentrated" and not the "absolute" should be employed, as the latter is insoluble in water. Ethyl butyrate, concentrated, is a clear colorless liquid and possesses a strong fruity (pineapple) odor. It is made from the absolute preparation by the addition of a small amount of pure alcohol. Tightly corked, it keeps well in the icebox. It has been used in from 2 to 6 per cent strength, in distilled water, in amounts ranging from 5 to 25 cc.

The blood is drawn as for the Wassermann test (three to four hours after eating) and, after thoroughly clotting, is placed in the icebox over night. As soon as possible after removal from the clot, 1 cc. of serum is placed in a sterile test tube, and 10 cc. of a 4 per cent solution of ethyl butyrate, concentrated, previously made neutral to phenolphthalein (with N/10 NaOH), is added. This indicator is used in the strength of 1 cc. of 0.5 per cent phenolphthalein in 50 per cent alcohol, per 100 cc. Usually, less than 1 cc. of the sodium hydroxide solution renders 100 cc. of the butyrate solution neutral. The addition of such small amounts does not seem to produce soap in any appreciable quantities. A smooth, faintly opalescent solution should be obtained. Finally, all tubes are individually neutralized, as the reaction of different sera varies slightly, and 0.3 cc. toluene is added to each to prevent bacterial growth. This amount of toluene does not interfere with the action of the enzyme. The tubes are then tightly stoppered as butyric acid is volatile, and incubated at 38°C. for twenty-four hours, when titrations are made to estimate the amount of butyric acid formed. The findings are recorded in terms of so many cubic centimetres of N/20 or N/50 NaOH, as the case may be. With each series of tests a control tube of ethyl butyrate solution alone (plus the toluene) is run, to estimate the amount of spontaneous hydrolysis. This is usually little more than a trace, but it may be deducted from the serum findings for greater accuracy. If the tubes are again incubated for a further period of twenty-four hours there is considerable further splitting of the ester, but never as much as during the first period.

Theoretically, repeated neutralizations and incubations should result in the complete hydrolysis of all the ester, provided the ferment is not destroyed before that time. Titerable acid is produced in progressively lessening amounts. About 1/60 of the ethyl butyrate (in 10 cc. of a true 4 per cent solution) is split up into butyric acid, when 1 cc. of N/20 NaOH is required to neutralize. Bradley (20) found the curve at first to be proportional to the square root of the enzyme, but later points along the curve may be proportional to any root of the enzyme. He stated that "the curve suggests rather a mass action of the enzyme upon the reaction similar to the mass effect of water in the hydrolysis of an unstable ester or in the ionization of a poor electrolyte." We have found that titration with less than 1 cc. amounts of serum, either with the usual (10 cc.) or correspondingly reduced amount of the substrate, gives results that are not proportional to the 1 cc. amounts, and thus cannot be used for comparison. Tests have shown that the major part of the hydrolysis occurs in the first seven hours of incubation for, after a certain point is reached, the acid formed inhibits the action of the enzyme. With the production of acid in sufficient amounts, the serum protein begins to be precipitated, and the precipitation increases, until the point of maximum acid formation is reached. Thus the amount of precipitate in each tube is roughly proportional to the acid titre; also, the more active the ferment, the sooner will precipitation begin. The question naturally arises whether there is sufficient hydrolysis or cleavage of the serum protein itself to materially increase the amount of titerable acid present at the end of the test. To determine this, tests were run, using guinea pig serum. It was found that, in a neutral solution, there is no hydrolysis of protein in twenty-four hours, but, when a certain amount of butyric acid is present, the occasional extra acid formed is insignificant and may be disregarded. The strengths of acid used approximated the usual range of the tests.

It has been our practice to chart the results in the form of an index taking the average findings of our control tests as 1 and expressing results in percentages, or in the form of a decimal fraction, just as the color index of the blood is reported. This made the charted results much easier to understand than if we merely gave our findings in terms of N/20 or N/50 NaOH. An index of 0.75 would thus mean that the blood in question showed a lipase activity three-fourths that of the estimated normal.

Table 1 (a) shows the lipase activity at different times of a healthy young man, aged 24, and weighing 180 pounds. This gives an average of 0.70 cc. in terms of N/20 NaOH, and we considered it to represent the maximum normal average amount of serum lipase activity. This blood was used as one of the controls in nearly all of our tests. Other controls gave very similar results, indicating that lipase activity in health is remarkably constant and very much the same among different individuals (see table 1 (b)).

The technique employed is very similar to that of Sagal, who used 2 instead of 4 per cent ethyl butyrate solution, and added no preservative to the tubes. With 10 cc. of substrate and 1 cc. of serum he found the average blood lipase value of 16 normal healthy persons to range from 0.9 to 1 cc. in terms of N/20 NaOH. This is somewhat higher than our normals. Sagal used no preservative and there may have been some breaking down, through bacterial activity, of the serum proteins, with a resultant increase in titerable acid. Four per cent ethyl butyrate does not inhibit the growth of ordinary contaminating bacteria. Whipple used 4 cc. of a 6.5 per cent ethyl butyrate solution for each cubic centimetre of serum, and found, after 24 hours in the incubator, the normal serum lipase activity to be from 0.4 to 0.6 cc. in terms of N/20 NaOH. He used 0.3 cc. of toluene. Von Hess, working with animals, used 25 cc. of a 5 per cent ethyl butyrate solution for every 1 cc. of serum, but incubated for only four hours. He found pig, sheep and goat serum to show only a small

TABLE 1

Lipase activity in normal persons

In terms of N/20 NaOH, incubated for 24 hours

(a) J. C.		(b)	
	cc.		*cc.*
6/25	0.75	H. W.	0.68
7/15	0.74	L. S.	0.70
8/13	0.67	G. K. A.	0.68
10/19	0.75	L. M.	0.72
10/25	0.71	W. A. B.	0.68
2/17	0.71		
3/10	0.64	Average of (a) is	0.71 cc.
6/18	0.74	Average of (b) is	0.69 cc.
6/30	0.73		

amount of lipase activity, whereas dogs gave a titre of from 0.3 to 0.5 cc. (N/20 NaOH). On the other hand, birds, such as the duck and the pigeon, showed tremendous activity, the former testing over 11 cc. and the latter 7 cc. One sheep tested by us showed a serolipolytic activity of only one-half that of the human blood, whereas serum from our guinea pigs titred approximately six times that of the human. It is obvious that with different strengths of the substrates varying results will be obtained with the same serum.

RESULTS

Our lipase findings in the study of over 150 bloods on admission are grouped together in table 2, in which they are arranged according to extent or stage of disease, activity of disease, loss of weight and admission prognosis. The first two groups are self-explanatory, and represent

the usual classification followed by most sanatoria. It was also considered important to determine the influence of loss of weight on the lipase, as in tuberculosis there may be early in the disease a diminution of the body fats. Finally, group 4 was included to determine the value of the lipase titre from a prognostic standpoint, as compared with the prognosis entered in the chart by the physician making the admission examination.

TABLE 2

General results

	NUMBER	INDEX AVERAGE	INDEX UNDER 0.80	POSITIVE SPUTUM	POSITIVE TUBERCULOSIS COMPLEMENT FIXATION
			per cent	*per cent*	*per cent*
(1) Stage:					
Minimal	12	0.92	none		
Moderately Advanced	76	0.86	22	77	71*
Far Advanced	73	0.78	48		
(2) Activity:					
Slight or none	76	0.88	21		
Moderate	63	0.83	34		
Serious	22	0.63	72		
(3) Weight (Loss from usual):					
No loss	67	0.88	19		
Up to 5 kg	36	0.87	25		
Over 5 kg	58	0.80	57		
(4) Admission Prognosis:					
Excellent	9	0.84	44		
Favorable	51	0.88	18 } 21.7		
Doubtful	21	0.78	52		
Unfavorable	19	0.68	63		
Hopeless	5	0.44	100		

* Only 3 and 4 plus considered positive.

A study of the table as a whole does not show as marked differences for each group average as one might be led to expect from the findings of other observers. This is largely explained by the fact that in the tuberculous we found the lipase titre to be much more variable than in normal persons. Quite frequently, even among those seriously ill, will be found an unusually high titre which naturally raises the average for that group. It is much more instructive to note the percentage of those with definite

reduction of lipase in each group. We have arbitrarily selected the index *0.80* as the lower limit of normal or nearly normal lipase activity and thus anything under this would indicate diminished lipolytic powers. In the last column in the table the percentage under 0.80 in each group is reported, which gives a much truer picture of conditions. Even at that, it will be noted that there is no marked reduction in the lipase titre until the patient is seriously ill. Under these conditions, however, approximately one-half of the far advanced and three-fourths of those with serious activity show definite diminution of lipase. Those who have lost most weight also show most loss in lipase. As the loss of weight usually parallels the intensity of the disease, it is not surprising that the lipase findings in group 3 should closely approximate those of group 1. In comparing the influence of extent of disease, amount of loss of weight and amount of activity, the last appears to be the most important in determining a low lipase titre.

In part 4 fewer cases are tabulated than in the rest of the findings. This part includes only those cases in which the prognosis was made by the same person. The results are somewhat confusing with regard to the first two groups but, if "excellent" and "favorable" be taken as one group, they will show approximately only one-fifth of their number with diminished lipase. This grouping closely approximates the groups showing no loss of weight and slight or no symptoms. When the prognosis is doubtful the lipase is also reduced in 50 per cent of the cases. In cases with definitely bad prognosis it is pretty generally reduced. What we are really reporting in this group is a comparison of our findings with one person's "guess" or forecast. It is interesting that there should be the agreement that the table indicates. The real prognostic value of the test can only be determined after a sufficient time has elapsed.

One-third of those with an index of 0.60 or less have died within the year. These constitute approximately three-fourths of all those dying within this time, as shown in table 3. As nearly all of these had been seriously ill for a considerable period before entering the Loomis Sanatorium, it is reasonable to suppose that, in most instances, the low lipase titre has been present for some time. Of those with a higher index than 0.60, case 5116 died suddenly from edema of the larynx, and case 5174 underwent an operative procedure which resulted in a rapid spread of his disease. If these be eliminated, it will be noted that in those dying in from a few days to three months the lipase index does not vary very much, the group average index being 0.45. The most that can be said

is that these low indices accompanying other evidences of serious disease are of grave import.

In table 4 are reported the findings in a few cases in which definite improvement was noted and on which one or more repeated lipase

TABLE 3

Those dying within one year

CASE NUMBER	LIPASE INDEX	TIME UNTIL DEATH	STAGE	TUBERCULOSIS COMPLEMENT FIXATION
5131	0.32	10 days	FAc	+
5139	0.35	3½ months	FAc	0
5111	0.36	5 days	FAc	+
5053	0.49	10 days	FAc	+
5086	0.50	2 months	FAc	0
5062	0.53	10 days	FAc	+
5036	0.60	1 month	FAc	0
5116	0.80	1 month	FAc	+
5022	0.81	11 months	MAb	0
5174	0.85	8 days	FAc	0
1968	0.96	10½ months	FAa	+

TABLE 4

Results in cases showing improvement

	CASE NUMBER									CONDITION
	5/25	8/4	10/18	11/16	11/27	12/18	2/26	4/6	6/1	
391	0.57			100						Much Improved
2080	0.71			100+						Much Improved
2104		0.49		0.85			0.92			Much Improved
4991	0.60					0.92				Much Improved
5046			0.68				0.99			Much Improved
5073							0.45	0.71		Slightly Improved
5061			0.59	0.98						Moderately Improved
5109					0.74		100+			Much Improved
5112					0.64	0.77	100	*	0.75	Improved to 2/26
5113					0.50	0.76	0.98			Much Improved
5143							0.80		100	Moderately Improved

* Tuberculosis of cecum: operated.

determinations were done. In every instance an improvement in the lipase activity also occurred. Case 5112 lost some of her gain as the result of tuberculosis of the cecum for which she was operated upon.

We have made no attempt to verify the findings of Bauer and Kollert and Frisch that in early tuberculosis an increase in lipase is found. Our

early cases were too few on which to base any conclusions. As a group they do not show the increase in lipase mentioned by these authors. However, in the few cases studied we were able to verify the findings of Kollert and Frisch with regard to the lipase value of tuberculous exudates.

In brief, our findings do not differ materially from those of other observers. The individual variability lessens the value of the test. Possibly the average of a series of determinations at short intervals would give a truer picture of the lipolytic activity of the tuberculous individual. Judging from results obtained from a single determination, the findings are of little prognostic value in cases in which just such information is most needed, namely, the early cases; and in the advanced cases they offer only additional evidence of what must be already plainly apparent to the clinician. From our limited experience it would seem that the lipase determinations parallel the condition of the patient, rising or falling as the disease improves or worsens. Apparently lipase change does not antedate alteration in the condition of the patient; it merely accompanies it.

DISCUSSION

In discussing the value of these results, because we can obtain, *in vitro*, hydrolysis of certain artificial fats, are we justified by analogy in assuming that foreign fats, such as tubercle bacillus fat, are broken down in the body by the body juices, just as a simple ester is similarly affected in the test tube? Generally speaking, the evidence is that all cleavage of the fat molecule, whether it occurs outside or within the cell, is activated by specific enzymes of the nature of whose activity comparatively little is known. The action of the pancreatic juice on ingested fats is a well-recognized example of such specific enzyme action. Tubercle or any foreign fat may well be attacked by a specific enzyme, but so far the evidence is not at all clear that this is the same enzyme that we are dealing with in our test tube experiment. In the latter something in the blood serum does break down the ethyl butyrate: *is it the same something*, only active to a much greater degree, that might attack and digest bacillary wax? It must not be forgotten that certain other compounds, such as proteins, requiring strong chemicals for their hydrolysis in the test tube, are easily broken down within the body.

Thus far the chief evidence that tubercle bacilli are destroyed in the body through lipolytic activity is that offered by the experiments of Bergel mentioned in the introduction. His deductions depend entirely

on the belief that lymphocytes are rich in lipase. He reasons that, because tubercle bacilli rapidly lose their acid-fast qualities on being ingested by the large mononuclears which he classifies as lymphocytes, this must be due to the fat-splitting ferment present in the lymphocytes, for the acid-fastness of the tubercle bacillus is dependent on the integrity of its fat. Bergel's (21) belief in the superior lipolytic activity of the lymphocytes rests in part on some experiments conducted by him in 1909. He reported having been able to demonstrate active fat-splitting ferments in the lymphocytes by his so called "plate" method. Tuberculous exudates and spleen and lymph node juice, when placed on plates of stearin, palmatin and wax, produced characteristic depressions, with crater-like hollows, which were interpreted as evidence of fat digestion. However, exceptions have been taken to this claim, and recently Reed (22) has shown that these so called depressions are simply mechanical, rather than the result of digestion, and are due entirely to the sinking in of the tested material while the plates were softened in the incubator.

Furthermore, Foot has definitely shown that the large mononuclear cells (macrophages) which, according to Bergel, play such an active part in the ingestion of tubercle bacilli, are not lymphocytes at all, but of altogether different origin, actually developing from the endothelium of the neighboring capillaries and migrating in steadily increasing numbers to the vicinity of the invading bacteria. These cells have a marked affinity for carbon in colloidal suspension, which makes their identification possible and enabled Foot to trace their course and development. He also has shown that in the tuberculous focus the lymphocytes appear relatively late, and that there is no evidence that they are transferred into these larger cells, the macrophages. Their rôle is a minor one. Finally, let us again refer to Long's denial that the loss of acid-fastness is due to lipolysis. In further explaining his views he states that the acid-fastness of the tubercle bacillus is largely dependent on the disposition of a portion of the wax in the cell protoplasm. For this disposition or combination of the wax and protein he uses the term lipin-protein, and points out that the acid-fastness of the bacillus cannot be due to the acid-fastness of a single substance, as wax, for bacilli, which have been dried and treated with fat solvents until 20 to 35 per cent of their dry weight has been removed, remain acid-fast; and again, bacilli from which no fat or lipin has been removed can be rendered nonacid-fast by mechanical disintegration, such as grinding in a mortar. Porter (23) tested the effect of different enzymes upon living bacteria of the

acid-fast group and found that the proteolytic ferments affected the staining properties of acid-fast bacilli much more profoundly than do lipolytic ferments.

It would seem from the findings of these more recent investigators that Bergel's theory is untenable and his experiments misinterpreted. It is now pretty clearly shown that (1) material rich in lymphocytes has no lipolytic effect on higher fats, (2) Bergel's so called lymphocytes are not lymphocytes at all but of absolutely different origin and (3) a true lipase fat reaction is not essential for the disruption of the tubercle bacillus with the accompanying loss of acid-fastness.

SUMMARY

The so called lipase or esterase, that we have been discussing and dealing with, may be a true lipase in the sense that it plays some part in the general fat metabolism of the body, but its relation to the destruction of the tubercle bacillus is very uncertain and not at all proved. It is present in many animals; in small amount in the slow-moving animals, such as the pig, sheep and goat, but in many times this amount in more active creatures such as the birds and fowls. We might look upon it as an index of functional activity, for it is apparently high when the metabolic powers are high and reduced when metabolism is sluggish. With the wasting and lessened functional activity, which accompanies advanced cases of tuberculosis, it is distinctly decreased, probably reaching its lowest point just before death. Apparently, the same thing is true of cancer and other wasting diseases characterized by cachexia. From the evidence at hand there is nothing to show that the lipase reduction is peculiar to tuberculosis, and represents the loss of a specific resistance factor. It might just as well be interpreted as evidence of the gradual weakening of the vital processes, of which the fall in lipase is but a single manifestation.

CONCLUSIONS

1. The identity of the serum lipase (esterase) with the true lipase is uncertain.
2. It is usually diminished in tuberculosis commensurate with the extent of the disease.
3. Single determinations have but little real prognostic value.
4. There is no real evidence that the serum lipase (esterase) is an active agent in the destruction of the tubercle bacillus.

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STUDIES ON THE RESPIRATORY ORGANS IN HEALTH AND DISEASE[1]

XII. THE EFFECTS OF BITUMINOUS COAL MINING ON THE VITAL CAPACITY OF THE LUNGS[2,3]

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A great deal has been written about the effect upon the lungs of the inhalation of various kinds of dust. Landis (1) has shown that they are divisible into organic and inorganic dusts. Organic dusts may be subdivided into animal and vegetable, while inorganic dusts are subdivided into metallic and nonmetallic forms. So far as direct injury to the lungs is concerned, organic dusts are insignificant; however, Landis calls attention to the fact that they may be the means of transmitting disease germs, such as the tubercle bacillus, directly to the lungs. Again it has been shown that the inhalation of certain organic dusts, both animal and vegetable, is capable of producing attacks of asthma.

Speaking of inorganic dusts Landis says:

> Briefly summarized, inorganic dusts, no matter what their source, produce definite changes in the lungs. They differ in the severity of the lesions produced in accordance with hardness, sharpness and chemical composition. At one end of the scale are the siliceous dusts, capable, under favorable conditions, of producing serious pulmonary damage in a comparatively brief period of time. At the other end are those which produce slight changes and then only after years of exposure. Among the latter may be mentioned plaster of Paris, lime, bituminous coal and soft carbonaceous material in the form of soot.

It is the popular belief among the laity that the inhalation of dust predisposes to tuberculosis. It has been shown, however, that the in-

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[2] Read in part before the Medical Staffs of the Lymanhurst School for Tuberculous Children and the Parkview Sanatorium, Minneapolis, June 26, 1923.

[3] This study was carried out with the aid of a grant from the Research Fund of the University of Minnesota.

organic dusts capable of causing the most serious pulmonary damage produce fibrosis, an important factor in the healing of a tuberculous process. Beattie (2) believes that in the occurrence of tuberculosis in those who inhale certain inorganic dusts the damage is produced only in "reducing the area of effective lung tissue and probably therefore encouraging the lodgment of tubercle bacilli."

Landis and others are of the opinion that the greatest danger from inorganic dust in relation to tuberculosis is that the particles are capable of carrying the tubercle bacillus into the body. Moreover, they impress the fact that we must never forget that tuberculosis is always caused by the tubercle bacillus and that the inhalation of dust alone will not produce the disease.

Klotz (3) has shown that pulmonary anthracosis may result from the inhalation of much coal smoke and soot and that this form of pulmonary anthracosis "is distinctly an urban disease, and is proportionate to the smoke content of the air." He points out further that small quantities of carbon deposits may be harmless, but larger quantities, such as those found in the lungs of large city dwellers, are productive of more or less fibrosis, which tends to impair the elasticity and consequently alter the functional capacity of the lungs.

Haythorn (4) concluded that moderate anthracosis is not detrimental to health provided there is no other disease in the lungs. He states further that, in tuberculosis and granulomatous conditions, anthracosis may actually assist healing in stimulating fibrosis and encapsulation of the lesion. He states also that anthracosis obliterates the lymph spaces and thus tends to localize the disease process. This obliteration of the lymph spaces is detrimental, however, in acute inflammatory diseases in which lympatic drainage is very important.

For a long time opinions have been expressed to the effect that coal miners develop less pulmonary tuberculosis than workers in many other occupations. Wainwright and Nichols (5) called attention to the statements of Kubon, of France, DeCrocq, of Belgium, Arnold, Seltmann, Goldmann and Hirt, of Germany, and Oliver, Trotter, Tatham and Parry, of England, that tuberculosis is a rare disease among coal miners. Goldmann and Trotter found that tuberculosis is more prevalent among miners' families and others living in mining districts than among the miners themselves. This finding was confirmed by Wainwright and Nichols, who, working in the largest anthracite centre in the United States, found that tuberculosis is about two-thirds less frequent among miners than among all other occupied men.

Wainwright and Nichols called attention to the fact that there is no crowding at work among miners, for usually there are not more than two or three men working in a large chamber. The danger of spread of infection among the men at work is reduced to a minimum, since there is enough moisture to prevent sputum from becoming pulverized. The air of the mines is comparatively free from bacteria. Living conditions are generally good, there being very little crowding, and a good part of the miner's free time is spent in the open air, working in gardens and walking to and from the mines. A daily bath is imperative. These authors found that the average length of life (barring trauma) for anthracite coal miners is 49.93 years as against 48.05 years for other occupied males in the same city.

Wainwright and Nichols believe that a factor of considerable importance in the low incidence of tuberculosis in coal miners is the proliferation of connective tissue resulting from the stimulation of the coal dust. They divide anthracosis into three stages, microscopically. In the first stage there is no thickening of connective tissues. In the second stage there is a definite increase in the connective tissue of the alveolar septa, the interlobular septa and around the ramifications of the bronchi. They found that the increased amount of connective tissue is "almost never sufficient to give signs of consolidation." Their third stage consists of those individuals who had been miners but had been out of the mines for several years before death. Although changes in the epithelium had disappeared, the connective tissue thickenings still remained in this stage.

Landis states that the severity of the lesions produced by inorganic dusts are in accordance with their hardness, sharpness and chemical composition. Therefore, one would expect greater damage to result from the inhalation of dusts from anthracite than from bituminous coal. From an excellent experimental study in which only soft coal dust was used, Willis (6) concluded that "There is some lymphoid tissue proliferation in response to the presence of dust, but no development of fibrous tissue during the period of a year in which the animals were exposed to dust." In regard to the effects of coal dust on the development of tuberculosis, he concluded that "After infection tubercle develops somewhat more abundantly in lungs of animals exposed to dust than in those of normal animals. The ratio is about as three to two."

Undoubtedly it is true that gross injustice has been done to some of the industries in which the workmen have in the past been compelled to

work in dust. Individuals, dying after such symptoms as cough and emaciation, are often reported as tuberculous with no confirmatory evidence. Even from the standpoint of X-ray examinations Jarvis (7) states that "It would seem that many densities are being diagnosed as tuberculosis which should be considered as densities of pneumonokoniosis."

With some of these facts in mind it seemed worth while to make an investigation of the functional capacity of the lungs of persons engaged in certain of the "dusty occupations." Therefore in the summer of 1920 I went to the Hocking Valley Coal Region for the purpose of making vital lung capacity observations on a few of the coal miners. The mines at which most of the readings were taken are located at Cannanville, near Athens, Ohio, and are operated by the Cannanville Coal Company. Permission was secured to make all observations at one of the company's stores, with the understanding that the procedures be entirely voluntary on the part of the miners. Observations were made on more than eighty men ranging in age from 17 to 73 years. The time that this group of men had spent as coal miners ranged from one week to 57 years, with an average of 16.7 years. Although physical examinations were not made, all men in this series were working and apparently in good health. Only one case of active tuberculosis was observed; however, several cases of asthma were brought by friends for examination. None of these cases are included in the group presented in this paper.

For this work the usual measurements were taken, including standing height, sitting height, chest circumference, body weight and vital lung capacity. In this group of individuals the vital lung capacity ranged from 6300 to 2500 cc. Attention is called to the fact that the man with a vital capacity of 6300 cc., although he had worked in the mines for eight years, had played a wind instrument a great deal over a period of eight years, having played every day for two years while in the army. From the wide variation observed in the vital capacity readings, and since vital capacity is influenced by such factors as age and size of the individual, it is obvious that all readings should be expressed in percentage of the theoretical normal. The percentage of the theoretical normal capacity was obtained from percentage tables (8), in which the calculations were made from observations and formulae of Dreyer (9) (10) and others (11) (12). Percentages, calculated from standing height, sitting height, chest circumference, body weight and surface area, were used.

The percentage of the normal, when calculated from body surface according to the method of West, averaged 91.4, while after the method

of Dreyer it averaged 93.4. It is interesting to note that when West compared these two methods on his series of college students he found approximately the same difference of 2 per cent. When sitting height and chest circumference formulae were used, the average was approximately 7 per cent higher and 6 per cent lower, respectively, than when surface area formulae were used. When the standing height method was used the average percentage of the normal was found to be 94.5.

Chart 1 shows a curve in which the percentage of normal vital capacity calculated from surface area is plotted against the number of years spent in the mines. Although there is a fairly wide variation in vital capacity, it will be observed that the average represented by the curve is in the neighborhood of 95 per cent of the normal until a period of 24 years has been spent in this occupation. Beyond this period the percentage of vital capacity is diminished considerably, for the most part being below 80 per cent of the normal and in one or two instances reaching as low as 65 to 70 per cent.

One must not overlook the fact, however, that with increase in years of service there is increase of the individual's age. It has been pointed out by Hutchinson (13), Peabody and Wentworth (14), West (11), McKean (15), Bowen (16) and Myers and Cady (17) that advancing years tend to reduce the vital capacity of the lungs. Bowen (16) found the greatest reduction occurring between the 50th and 60th years of life. With the effect of age on vital capacity in mind, chart 2 was produced by plotting age against vital capacity percentage. This curve shows that the group below the age of 22 years presented an average vital capacity of approximately 88 per cent. Hutchinson (13) stated that the maximum vital capacity is reached at the age of 30 years. However, the recent studies of Stewart showed that the maximum for boys probably is reached about the twentieth year of life. According to this last statement, the low vital capacity of my small group younger than 22 years cannot be explained on an age basis. Between the ages of 22 and 34 years the vital capacity closely approaches 100 per cent of the normal. Between the ages of 34 and 46 years it ranges between 90 and 95 per cent of the normal, while beyond the age of 46 it is for the most part below 90 per cent of the normal. From the ages of 58 to 73 years the average vital capacity is between 60 and 70 per cent of the normal.

A comparison of charts 1 and 2 shows that there is only a slight difference between the curves. Dreyer and others have pointed out that a

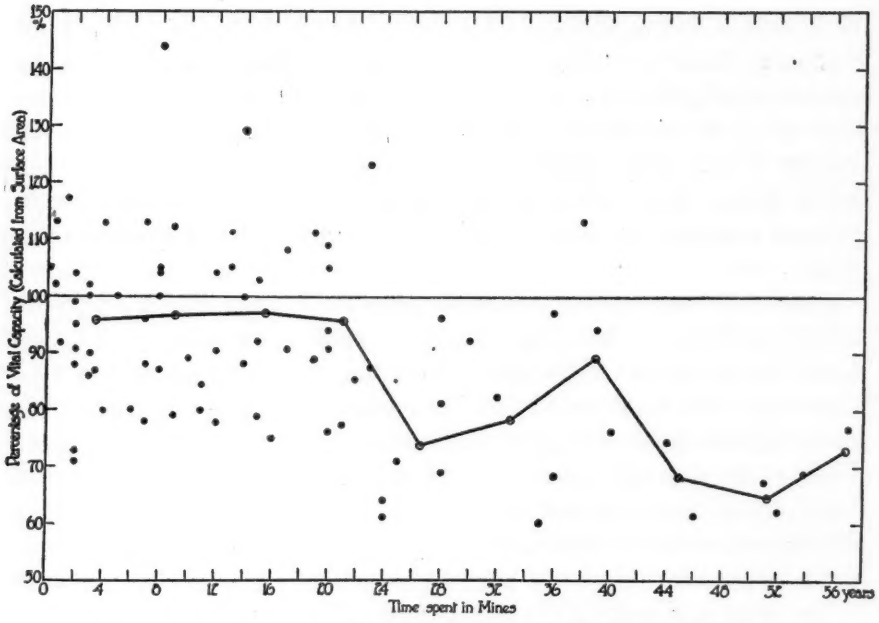

CHART 1. VITAL CAPACITY PLOTTED AGAINST TIME SPENT IN MINES

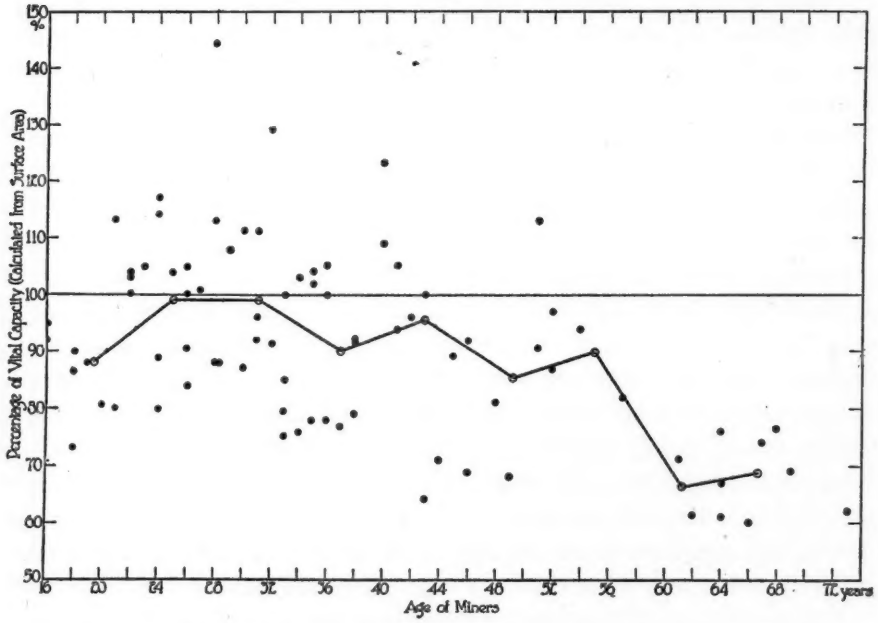

CHART 2. VITAL CAPACITY PLOTTED AGAINST AGE OF MINERS

vital capacity of 90 per cent or above may be considered normal, while a capacity between 85 and 90 per cent should make one suspicious of some abnormal condition, and a capacity below 85 per cent of the theoretical normal nearly always is indicative of some abnormality, usually of the lungs or heart. With these statements in mind, it is obvious from the curves that the group of this series of coal miners younger than 46 years and the group that have been in the mines less than 24 years have vital lung capacities which average well within normal limits. After the age of 46 years most of the readings are below normal limits. However, this reduction is explainable on the age basis and it is very questionable if occupation plays any considerable rôle.

In 149 Minnesota people (18), representing many occupations and at various ages, examined and found negative for pulmonary tuberculosis, the vital lung capacity averaged 103.6 per cent of the normal, while 100 other cases suffering from chronic bronchitis presented an average vital lung capacity of 103.0 per cent of the normal. These percentages were obtained from Dreyer's body weight formula, and when compared with those of the bituminous coal miners obtained from the same formula there is a difference of approximately 10 per cent in favor of the Minnesota group. From these comparisons it would appear that bituminous coal mining tends to reduce slightly the vital lung capacity. However, sight must not be lost of the fact that we are making comparisons of individuals living in entirely different localities and that physical examinations of the miners were not made.

SUMMARY

1. Vital lung capacity observations were made on approximately 80 bituminous coal miners whose ages ranged from 17 to 73 years. The time spent in this occupation ranged from 1 week to 57 years with an average of 16.7 years.

2. The average vital lung capacity calculated from surface area, according to the methods of Dreyer and West, was 93.4 and 91.4 per cent of the normal, respectively.

3. No appreciable decrease in capacity was observed below the age of 46 years, or 24 years of service in the mines. The lower averages after these periods were attributed more to advancing age than to occupation.

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STUDIES ON THE RESPIRATORY ORGANS IN HEALTH AND DISEASE[1]

XIII. THE EFFECTS OF SENILITY ON THE VITAL CAPACITY OF THE LUNGS[2,3]

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Minneapolis

Hutchinson (1) called attention to the fact that age influences the vital capacity of the lungs. He said, "The vital capacity therefore . . . . increases with the age up to 30 years, and from 30 to 60 it decreases 42 cubic inches."

Wintrich (2) in 1854 made observations on a large number of men and women. In his paper he gave considerable consideration to the effects of age on vital capacity. He found that a slight decrease in vital capacity appears between the ages of 40 and 50 years. A marked decrease was observed between the ages of 50 and 60 years, which he believed to be due to the beginning of body wasting and the appearance of obesity. In muscular old people, of 64 years and above, he found the vital capacity the same as in individuals between 45 and 55 years. After the seventy-sixth year he observed a striking decrease in vital capacity to the level of puerile individuals. He found further that old women decrease less rapidly than old men in vital capacity, but the sex difference is maintained, nevertheless, up into the highest ages.

Arnold (3) in 1855 studied a good-sized group of individuals, and, as regards the effects of age on vital capacity, he agreed with Hutchinson. He believed, however, that the number of individuals studied was not sufficient to draw any sweeping conclusions.

In an inaugural dissertation on vital capacity published in 1884, Cornet (4) stated that after the age of 35 years the vital capacity decreases 30 cc. per year.

[1] From the Department of Preventive Medicine and Public Health and the Department of Internal Medicine, University of Minnesota.

[2] Read before the combined medical staffs of the Parkview Sanatorium and the Lymanhurst School for Tuberculous Children, June 26, 1923.

[3] This study was carried out with the aid of a grant from the Research Fund of the University of Minnesota.

In 1917 Peabody and Wentworth (5) in discussing vital capacity, stated that "weakness and old age may cause a slight decrease."

West (6) in 1920 said, "In addition, it is very desirable that more observations be made on elderly individuals, for age apparently reduces the vital capacity to an appreciable extent."

McKean (7), from personal observations in a considerable number of persons over forty years, states that "there seems to be a decrease normally to 75 or 80 per cent of the normal standards for younger adults, as the tissue elasticity grows less."

Myers (8)(9)(10) mentioned the reduction of vital capacity with age in connection with studies on other phases of the vital capacity of the lungs.

Levine (11), in considering a series of cardiac cases, states that "The vital capacity diminishes even in normal persons with advancing years; and since the patients we are considering are a great deal older than those used in previous standards, no accurate figures could be deduced. This will be impossible until a large series of normal elderly persons are studied and their vital capacity determined."

In discussing the influence of age on vital capacity, Pratt (12) says

> The vital capacity is definitely influenced by the age of the subject. It reaches its maximum in the third decade. . . . in the fourth decade the average vital capacity falls slightly. . . . . A marked lowering in the vital capacity was not noted in my series until after the age of sixty. The 11 men who were between the age of sixty and seventy, when tested, showed an average vital capacity of only 73 per cent of West's standard. Above the age of seventy I have examined only three men with apparently normal hearts. They had no shortness of breath on exertion, but their vital capacity was much reduced, being only 56 per cent of the normal. The number of cases in this decade is too small to permit of drawing any conclusions from the figures given. When more persons above seventy are examined the average percentage may be lower or higher.

Bowen (13) recently reported the results of his studies on the relation of age and obesity to vital capacity. Twenty-five of his cases were between the ages of 50 and 60 years, while 39 cases were 60 years or older. His remaining 120 cases were between the ages of 15 and 50 years. In this work Bowen employed the height and surface area standards. He found that up to the age of 50 years the average vital capacity was 95.8 per cent of the normal. "Then it gradually reached 50 per cent at

the age of 85 years; the greatest fall in any decade being between the ages of 50 and 60 years."

Considerable interest was aroused in the vital capacity of the lungs in senile individuals in 1920, while taking readings in a group of bituminous coal miners (14) some of whom had passed considerably the sixtieth year. Since that time we have been compiling the data presented in this report.

OBSERVATIONS

Our observations were made on 206 subjects of whom 88 were women and 118 were men. The ages of the women ranged from 66 to 87 years, and those of the men from 66 to 89 years. All were active and apparently in good health at the time the observations were made.

The Sanborn spirometer was used throughout. In all cases from three to five readings were taken, and the highest was recorded as the vital lung capacity.

The percentages of the normal vital capacity were obtained from percentage tables and charts (15) calculated from stem length, Dreyer's (14) (15) weight formula, standing height and surface area.

The average vital capacity of the group of women, when calculated from surface area, was found to be 50.7 per cent of the normal. From Dreyer's (17) weight formula the average vital capacity was 49.4 per cent of the normal. From the stem length formula it was 53.2 per cent of the normal, while from the standing height it was 49.8 per cent. It will be seen that there is a difference of only 1.3 per cent between the averages calculated from the surface area method of West and the body weight formula of Dreyer. In comparing these two methods, West found that Dreyer's method resulted in about 2 per cent lower averages than when the surface area formula of Du Bois and Du Bois (18) was used. In a group of bituminous coal miners it was shown that the two methods gave results with a difference of exactly 2 per cent. The recent work of Boynton (19) on 738 college women showed a difference approximately of 3 per cent between these methods. Inasmuch as surface area is given consideration in Dreyer's body weight formula and the results obtained from this and West's method differ so slightly, it is obvious that it makes very little difference which method one employs.

Cripps, Greenwood and Newbold (20), after an extensive biometric study of vital capacity, concluded that "The substitution of stem length for height does not improve the accuracy of prediction and, with the

minor exceptions noticed above, Hutchinson's method is as good or better than its recent modifications."

Rogers (21), from a study of 400 male students, concluded that "The correlation between stem height (Dreyer) and vital capacity was not significantly better than the correlation between standing height and vital capacity." On the other hand, Dreyer believes that stem length is a very valuable measurement in estimating the normal vital capacity of an individual. In this group of senile women there is a difference of 2.4 per cent between the average vital capacities calculated from stem height and standing height.

In our group of senile men, the average vital capacity percentages were 63.9, 64.7, 66.5 and 74.3 when calculated from surface area, Dreyer's body weight formula, standing height, and stem length respectively. Here it will be seen that a difference of only 0.8 per cent exists between the averages of capacities obtained from the methods of Dreyer and West. There is a difference of 7.8 per cent, however, between the averages of capacities calculated from standing height and sitting height.

Chart 1 shows that the curve representing women is distinctly lower than that representing men. In neither case is there a rapid decrease in vital capacity after the age of 66 years. The main part of the curve for our group of men begins at 73.8 per cent and ends at 52.9 per cent, while that for women begins at 52.1 per cent and ends at 44.2 per cent. Bowen's cases (13) are indicated in chart 1 but have not been included in the curves. In men the curves show a tendency to rise in the oldest ages observed. It is probable that this is due to the fact that only a very limited number of cases were observed at these ages, and it so happened that their percentages of normal vital capacity were quite high.

Chart 2 shows graphically the results obtained from the use of four different standards. It will be seen that the curves representing the percentages obtained from stem length deviate considerably from the other curves.

In this group of cases there were found 32 women and 32 men who were definitely "overweight." The number of persons "overweight" was especially high among those who had lead semiretired or retired lives for a number of years.

Bowen states that in "obese and 'overweight' people it is probably better to use the height standard or make a correction by adding 20 per cent to the surface area standard." By the surface area standard our group of "overweight" senile women showed an average vital capacity

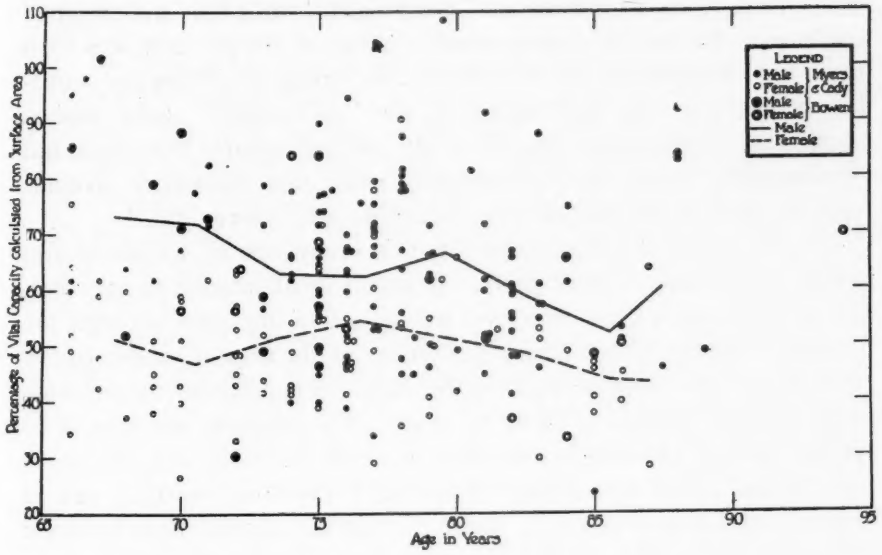

CHART 1

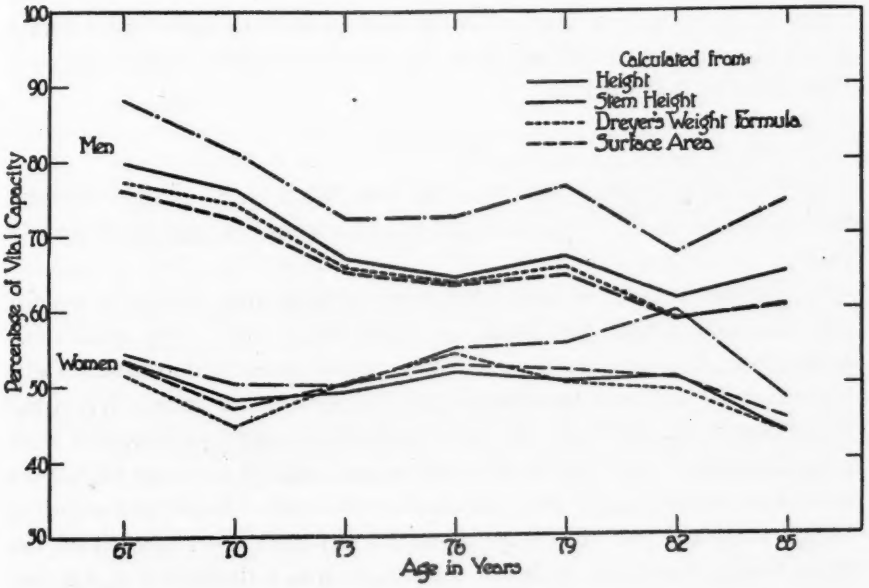

CHART 2

of 5.9 per cent less than those not "overweight," while the "overweight" senile men showed an average vital capacity of 6.8 per cent, less than those not "overweight" by the surface area standard. When the standing height standard was employed, the "overweight" senile women showed an average vital capacity of 0.7 per cent greater than those not "overweight," while the "overweight" senile men showed an average vital capacity of 2.0 per cent less than those not "overweight."

Several of the individuals used in this study one of us has known personally for more than 25 years. It was of great interest to note that, for the most part, those who have led an active life, even through the period of senility, have a higher percentage of the normal vital capacity than those who, because of favorable financial conditions, retired from active life at the age of 55 or 60 years. For example, one man of 75 years who had indulged in hard farm work all of his life and who spent his "spare" time in summers operating a threshing machine and in winters operating a saw mill, stated that at the present time he never misses a day at hard work. His vital lung capacity was found to be 4150 cc., which is well within normal limits for a man of the same size in the prime of life. This and a number of similar cases indicate that old age in itself should not justify retirement from active life. Moreover those who continue to lead a life of usefulness until some unfortunate physical conditions overtake them enjoy a much more happy existence than their retired friends.

SUMMARY

1. Vital lung capacity observations were made on 88 women between the ages of 66 and 87 years and 118 men between the ages of 66 and 89 years.

2. Normal standards calculated from surface area, Dreyer's weight formula, stem length and standing height were used. The results obtained from the surface area and Dreyer's weight formula showed a difference of 1.3 per cent for women and 0.8 per cent for men. When the stem length standard was used the resulting average percentages were approximately 3 per cent higher for women and 10 per cent higher for men than when surface area standards were used. From the standing height standard the women averaged 2.4 per cent lower than from the stem height standard, while for men there was a difference of 7.8 per cent. In both groups the results obtained from the standing height standard more closely approximated those obtained from the surface area

and Dreyer's weight formula standards than those from the stem length standard.

3. The vital lung capacity percentages for senile women average considerably lower than those for senile men. In neither group was there a rapid decline after the age of 66 years. The decline is gradual; in fact, our group of men began with an average of approximately 74 per cent and ended with an average of approximately 53 per cent of the normal vital capacity, while the group of women began with approximately 52 per cent and ended with approximately 44 per cent of the normal vital capacity.

4. Thirty-two of the women and 32 of the men were definitely "overweight." Their vital capacity averaged 5.9 per cent less for the women and 6.8 per cent less for the men by the surface area standard than individuals of corresponding ages but more closely approximating normal body weight. Vital lung capacity determined by standing height as compared with surface area gave values of 0.7 per cent for "overweight" senile women and 2.0 per cent for "overweight" senile men less than values for those approximating normal weight.

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HEMATOLOGICAL STUDIES ON EXPERIMENTAL TUBERCULOSIS OF THE GUINEA PIG[1]

II. THE EFFECT OF CERTAIN DRUGS ON THE BLOOD PICTURE IN TUBERCULOSIS

STUDIES ON THE BIOCHEMISTRY AND CHEMOTHERAPY OF TUBERCULOSIS. XXXI.

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In the first paper of this series (1) we studied the blood picture in nontreated tuberculosis of the guinea pig and concluded in part that:

1. Normal guinea pigs have a very uniform blood picture, particularly characterized by a seasonal variation of the hemoglobin content of the red cells, a high lymphocyte count, and a high eosinophile count coincident with the appearance of Kurloff bodies.
2. An acute infection with tuberculosis produces a characteristic blood picture, in which there is a rapid loss in erythrocytes with a relatively greater decrease in hemoglobin, a terminal leucocytosis or leucopenia, a progressive decrease in lymphocytes, a moderate preterminal increase in endothelial cells, and an absence of eosinophiles.
3. Chronic tuberculosis produces a blood picture quite different from that of acute tuberculosis. It is characterized by a fluctuation in all elements, a relatively low hemoglobin content of the erythrocytes which is not progressive but shows the normal seasonal variations, and absence of any reaction of the lymphocytes, and an eosinophilia which cannot, however, be distinguished from that associated with Kurloff bodies.

The original paper gives in full the methods and technique used, charts and tables of results, and discussions of the Kurloff bodies. The same methods have been now applied to the treated animals. The treatments employed have all been chemotherapeutic. For the chemistry of these drugs, their bactericidal powers, methods of treatment and effects on the

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tuberculous animals, reference should be made to other papers by DeWitt (2) (3). It is the purpose of this paper to study only the blood pictures of the animals that were being treated, and to determine whether the drugs in any way affected the usual changes in the blood picture that have been observed to occur in tuberculosis.

The animals which were examined had been treated with the following drugs:

1. No. 29. Paranitro-orthoacetoxymercuri-monomethylaniline.
2. Methylene blue.
3. Mercuric chaulmoogric acid.
4. No. 44A. Mercurized methylene blue.
5. New methylene blue GG.
6. Neutral red.
7. No. 56. 4-hydroxy-3-5-diacetoxymercuri-trimethylphenylammonium acetate.
8. No. 27 L.C. Mercuri-bis-3-3′hydroxy-5-5′trimethylphenylammoniumacetate.

Nontreated tuberculous animals were examined with each set as controls, and in some cases nontuberculous treated animals were also examined. The routine blood examination was made on each animal usually once in two weeks throughout the period of their infection and treatment.

1: No. 29. Paranitro-orthoacetoxymercuri-monomethylaniline: Four guinea pigs which were being treated with this drug were examined, as well as 4 nontreated tuberculous controls and 5 nontreated, nontuberculous controls. The infection was of the chronic type, all of the animals living for at least one year after the inoculation, and the blood picture of the nontreated controls showed the typical blood changes of chronic tuberculosis. Typical results in these animals are given in chart 1. The results of the blood examinations of the nontreated guinea pigs, both the tuberculous and the nontuberculous, were reported in the first paper of this series.

The important difference in the blood picture of the treated and the nontreated animals was that the usual eosinophilia did not appear in the treated guinea pigs. As all of the animals had Kurloff bodies, there was an eosinophilia in the nontuberculous controls as well as in the tuberculous controls. Thus, in 4 nontreated tuberculous guinea pigs the average eosinophile count for one year (59 examinations) was 140 per cmm. of blood with 460 per cmm. as the maximum figure. In 4 treated tuberculous animals the average for the same period (56 examinations)

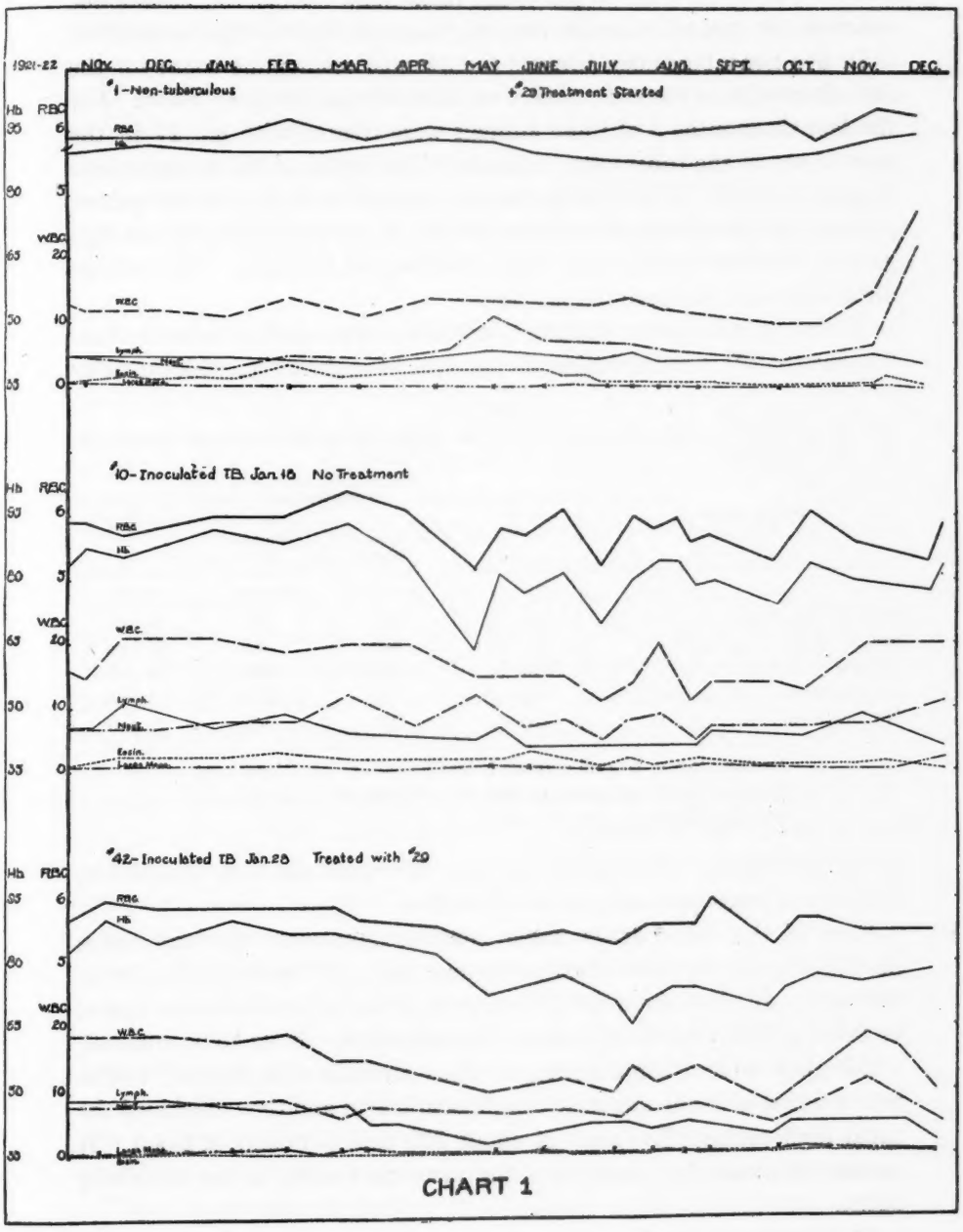
1921-22
NOV. DEC. JAN. FEB. MAR. APR. MAY JUNE JULY AUG. SEPT. OCT. NOV. DEC.
#1 - Non-tuberculous
+#29 Treatment Started
Hb RBC
WBC
#10 - Inoculated TB. Jan. 18 No Treatment
#42 - Inoculated TB. Jan. 28 Treated with #29

CHART 1

was 25 per cmm. with 80 per cmm. maximum. Thus the eosinophile count of the treated animals was only 16.4 per cent of the nontreated.

In five nontuberculous animals the average eosinophile count for the first six months of the same period was 300 cells per cmm. of blood. For the last six months 3 of these animals were treated with no. 29 in the same doses as the tuberculous animals. The results of the treatment are shown in table 1. The average loss in eosinophiles in the treated guinea pigs for the six months after treatment was 21 per cent while the average gain in the untreated for the same time was 46 per cent. The average difference was therefore 67 per cent.

We may conclude that paranitro-orthoacetoxymercuri-monomethylaniline has the effect of inhibiting the increase of eosinophiles which usually

TABLE 1

Showing the effect of treatment with No. 29 on the eosinophiles of nontuberculous guinea pigs

TREATMENT NO. 29	ANIMAL	AVERAGE NUMBER OF EOSINOPHILES		GAIN OR LOSS
		Six months before	Six months after	
		per cmm.	*per cmm.*	*per cent*
Started June 1.....	No. 1	235	133	44 loss
Started June 1.....	No. 45	465	315	35 loss
Started June 1.....	No. 46	510	610	16 gain
No treatment.....	No. 3	40	110	64 gain
No treatment.....	No. 20	248	345	28 gain

Average loss in treated animals in last 6 months = 21 per cent.
Average gain in untreated animals in last 6 months = 46 per cent.
Average difference = 67 per cent.

occurs in chronic tuberculosis and also decreases the high eosinophile count in animals possessing Kurloff bodies.

Four of the other drugs under consideration were mercury salts: no. 27L.C., no. 56, mercurized methylene blue, and mercuric chaulmoogric acid. In all of these cases the course of the tuberculosis was acute; in this condition we would expect the eosinophile counts to be minimal, which they were. Some nontuberculous animals with Kurloff bodies were treated with the mercuric chaulmoogric acid and they displayed the usual high eosinophile count of about 200 cells per cmm. of blood. It cannot be concluded, then, that the mercury moiety is the inhibiting agent.

2: Methylene blue: Ten tuberculous and 3 nontuberculous animals, which were being treated with methylene blue, were examined. The

inoculated guinea pigs had acute tuberculosis, and most of them died of the disease or of acute secondary infections before many examinations could be made. Thirty-five examinations were made on the 10 animals, 9 of which were made on one animal. The leucocyte counts of these guinea pigs were high, but a leucocytosis was prevailing among all of the laboratory guinea pigs at the time, and these animals which were being treated with methylene blue in no way differed from the other acutely tuberculous guinea pigs. It appears that methylene blue had no effect on the blood picture in acute tuberculosis or in the uninoculated guinea pigs.

3: Mercuric chaulmoogric acid: Ten tuberculous and 3 nontuberculous animals were treated with this drug. The disease was of the same type as in those animals that were being treated with methylene blue just discussed. Blood pictures were similar, showing the prevailing leucocytosis. The drug appeared to have no effect on the blood picture of either the tuberculous or the nontuberculous animals.

4: No. 44A. Mercurized methylene blue: Blood examinations were made on 8 animals that were being treated with this drug. Five nontreated tuberculous animals were also examined as controls. A total of 41 examinations was made. Acute secondary infections caused the death of all but 2 guinea pigs of each set. Acute generalized tuberculosis was the cause of death in the latter. It will be seen from chart 2 and table 2 that the treated animals showed a more severe anemia than the nontreated, and that in those which survived the acute infections and died of tuberculosis the hemoglobin reached the levels of 52 and 30 per cent, the latter being the lowest hemoglobin percentage on record in our tuberculous guinea pigs. The number of erythrocytes also reached a low level, the lowest figure being 2,800,000 in the treated as compared to 5,200,000 in the untreated. The leucocyte count of the treated animals never reached the high level of the untreated animals, the maximum count being 18,000 in the treated and 40,000 in the untreated. Since the average length of life in the treated was shorter than the untreated (2.23 months as compared to 3.13 months), and autopsies showed that acute secondary infections were apparently equally severe in both cases, it would appear that the low leucocytosis was not due to less infection in the case of the treated animals but to an inhibited reaction to the infection.

Thus, mercurized methylene blue seemed to act as a poison to the blood, and especially to those elements which are formed in the bone marrow. That this action was not due to the mercury is shown by the

results of no. 29, no. 56, no. 27LC, and mercuric chaulmoogric acid, none of which had any effect on the erythrocytes or the leucocytes. Methylene blue itself did not inhibit leucocytosis or increase the anemia.

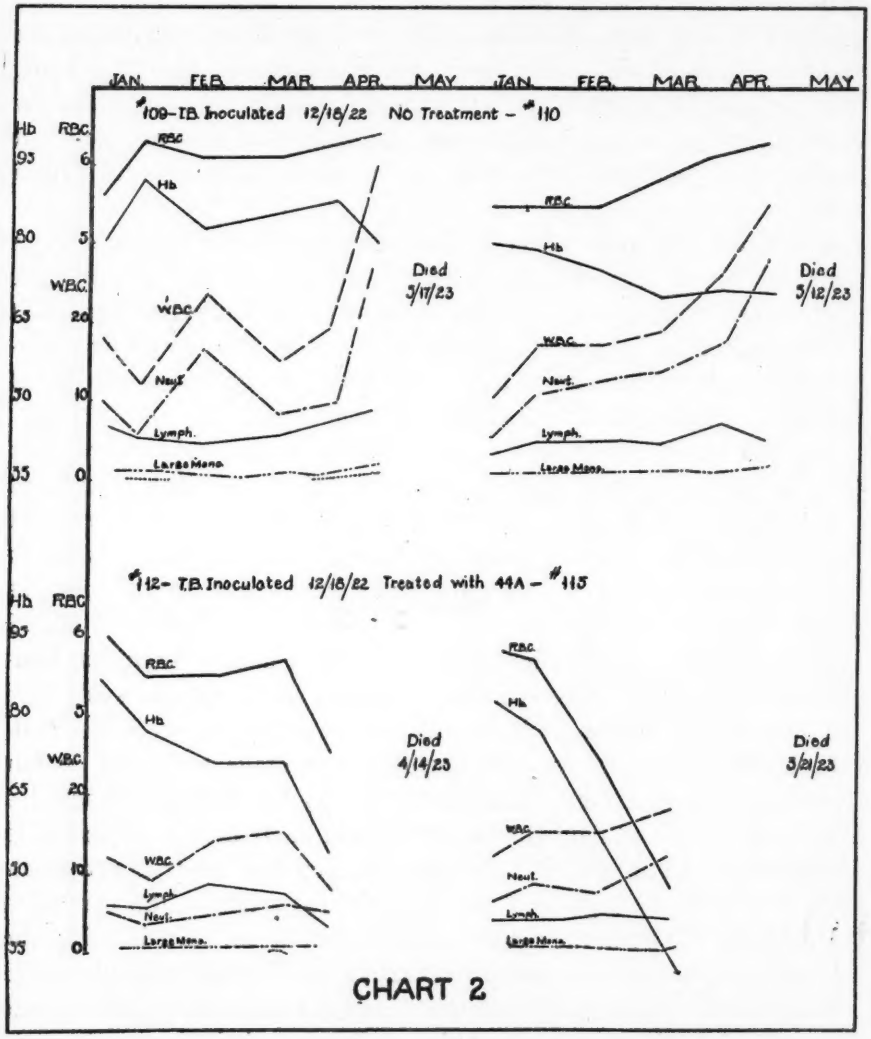

CHART 2

5: New methylene blue GG: Fourteen examinations were made on 5 animals which were being treated with new methylene blue GG. All of these succumbed to secondary infections. The tuberculosis, as far as it had developed was acute. There was no evidence that the treatment in any way affected the course of the blood changes in the disease.

6: Neutral red: Eight examinations were made on the 5 guinea pigs which were being treated with neutral red. These animals had acute tuberculosis but died of acute secondary infections, and the blood pictures revealed no changes due to the drug.

7: No. 56. 4-hydroxy-3-5-diacetoxymercuri-trimethylphenylammoniumacetate and *no. 27L.C. Mercuri-bis-3-3'hydroxy-5-5'trimethylphenylammoniumacetate:* Animals treated with these drugs were examined by Miss Ruth McKinney. Five animals were treated with no. 27L.C. and five with no. 56, and there were 3 treatment controls for each set. There were 4 tuberculous controls for both sets. The examinations covered a period of five months. In neither set could Miss McKinney find any difference in the blood picture due to treatment.

TABLE 2

The effect of mercurized methylene blue on the blood picture in tuberculous guinea pigs

	NUMBER OF ANIMALS	AVERAGE LENGTH OF LIFE	AVERAGE TERMINAL W.B.C.	AVERAGE TERMINAL R.B.C.	AVERAGE TERMINAL Hb.
		months			*per cent*
Treated.....	8	2.23	10,000	4,550,000	64
Untreated.....	5	3.13	25,000	5,880,000	75

CONCLUSIONS

1. No effect on the blood picture in tuberculous animals nor in nontuberculous controls could be demonstrated with treatment by methylene blue, mercuric chaulmoogric acid, new methylene blue GG, neutral red, no. 56, or no. 27L.C.

2. No. 29. Paranitro-orthoacetoxymercuri-monomethylaniline prevented the development of an eosinophilia in guinea pigs with chronic tuberculosis and decreased the eosinophile count in nontuberculous animals with Kurloff bodies.

3. No. 44A. Mercurized methylene blue seemed to act as a poison on those elements of the blood which are produced in the bone marrow, increasing the anemia and inhibiting leucocytosis in acutely tuberculous animals with secondary infections.

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THE DIAPHRAGMATIC EXCURSION AND MEDIASTINUM IN THE LATERAL RECUMBENT POSTURE[1]

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In 1921, one of us (G.B.W.), with Forster and Gilbert (1) published under the title *Postural Rest for Pulmonary Tuberculosis* a report on roentgen studies of the chest in lateral recumbency.

In 1922, Adams and Pillsbury (2) published an article entitled *Position and Activities of the Diaphragm as Affected by Change in Posture.* These authors confirmed our observations as to the wide range of the heart position (the extreme excursion being 6 cm.). They also concluded, "In lateral recumbency the dependent lung is relatively relaxed. Its diaphragmatic ventilation is in excess of that of the upper lung."

Hofbauer and Holzknecht (3) some years ago noted that, with a subject lying on one side, the half of the diaphragm on the dependent side made a larger excursion and was relatively higher than the upper half. This we confirmed, but we also noted that the increase of excursion of the lower half of the diaphragm does not continue indefinitely, but diminishes after an hour or less, and then the excursion of the two halves is approximately the same.

The present contribution deals with a continuation of such observations, and confirms fully the fact that after a short time the diaphragmatic ventilation of the recumbent lung is not in excess of that of the upper lung.

The subjects were studied with the flouroscope and were all normal young men between seventeen and twenty-two years of age.

	AT BEGINNING		AFTER 50 MINUTES
	mm.	*mm.*	*mm.*
1. *Subject on right side:*			
Right diaphragm excursion.....	11		12
Left diaphragm excursion.....	13½		18

[1] Read before the Association of American Physicians, Atlantic City, New Jersey, May, 1923.

	AT BEGINNING	AFTER 55 MINUTES	AFTER 75 MINUTES
2. *Subject on right side:*			
Right diaphragm excursion.....	22½	18	18
Left diaphragm excursion.....	18	22½	22½

	AT BEGINNING	AFTER 30 MINUTES	AFTER 60 MINUTES
3. *Subject on right side:*			
Right diaphragm excursion.....	10½	4½	4½
Left diaphragm excursion.....	9	10½	10½

	AT BEGINNING		AFTER 30 MINUTES
4. *Subject on right side:*			
Right diaphragm excursion.....	7½		7½
Left diaphragm excursion.....	9		16½

	AT BEGINNING		AFTER 30 MINUTES
5. *Subject on right side:*			
Right diaphragm excursion.....	18		12
Left diaphragm excursion.....	24		18

	AT BEGINNING		AFTER 30 MINUTES
6. *Subject on right side:*			
Right diaphragm excursion.....	8		13½
Left diaphragm excursion.....	24		24

	AT BEGINNING		AFTER 60 MINUTES
7. *Subject on right side:*			
Right diaphragm excursion.....	21		16½
Left diaphragm excursion.....	16½		18

	AT BEGINNING		AFTER 60 MINUTES
8. *Subject on right side:*			
Right diaphragm excursion.....	19½		16½
Left diaphragm excursion.....	11		22½

	AT BEGINNING	AFTER 30 MINUTES	AFTER 60 MINUTES
9. *Subject on left side:*			
Left diaphragm excursion.....	10½	9	9
Right diaphragm excursion.....	16½	15	15

	AT BEGINNING	AFTER 30 MINUTES	AFTER 60 MINUTES
10. *Subject on left side:*			
Left diaphragm excursion.....	22½	21	21
Right diaphragm excursion.....	19½	19½	21

	AT BEGINNING		AFTER 55 MINUTES
11. *Subject on left side:*			
Left diaphragm excursion.....	18		18
Right diaphragm excursion.....	22½		18

	AT BEGINNING	AFTER 30 MINUTES	AFTER 60 MINUTES
12. *Subject on left side:*			
Left diaphragm excursion.....	21	16½	15
Right diaphragm excursion.....	22½	18	16½

Adams and Pillsbury concluded that breath, voice and whisper sounds and tactile fremitus were all increased in the dependent lung as compared with the opposite side.

The following notes were made regarding respiratory sounds:

1. *Subject on left side:*
   At the end of one hour the vesicular murmur was decidedly more distinct at the front and the back of right apex.
2. *Subject on left side:*
   At the beginning breath sounds were more audible and distinct over right upper portion of chest. At the end of one hour breathing very quiet on both sides.
3. *Subject on left side:*
   At the beginning and after fifty-five minutes the vesicular murmur most distinct over front of right apex. Breathing at both bases very quiet.
4. *Subject on left side:*
   Breath sounds at the beginning and at the end of an hour more audible front and back over right apex.

5. *Subject on right side:*
   At the beginning the vesicular murmur was more distinct at back of left apex than on right. Breath sounds in front about equal. Breathing at bases front and back very quiet. After an hour the vesicular murmur was still more distinctly audible at the back of left apex. No differences noticed in front. Breathing at bases front and back very quiet.
6. *Subject on right side:*
   After one hour vesicular murmur most distinct at back of left apex. In front the breath sounds were equal in intensity. Breathing at bases very quiet front and back.
7. *Subject on right side:*
   After five minutes it was noted that the breathing at the front of right apex decreased in intensity when compared with same area of left lung. No difference noted in breath sounds at bases.
8. *Subject on right side:*
   At the beginning the breath sounds at the right base were a little more audible than those at left base. Breathing at the apices the same on both sides. The intensity of breath sounds at the front of the right apex less distinct than over the same area on left side.
9. *Subject on right side:*
   After thirty minutes the breathing on both sides was quiet, the right side being generally the quieter.
10. *Subject on right side:*
    After lying in this position for thirty minutes, breath sounds in front over right apex were a little quieter than over left apex. In the lower parts of chest there was no change. At the back to the third dorsal spine the breath sounds were equal in intensity on the two sides. Below this the breath sounds on the recumbent side were more audible.
11. *Subject on right side:*
    The diaphragm at the beginning showed greater excursion on the right than on the left; therefore the breath sounds at the base were intensified on the right. At the end of fifteen minutes diaphragm of dependent lung still showed greater excursion and breath sounds at the right base were still more audible than at the left base. At the apex in front the sounds were more audible on left side. At the end of thirty minutes the breath sounds were much more quiet at the right apex than at the left. Otherwise, the breath sounds were very quiet throughout both sides.
12. *Subject on right side:*
    At the beginning breath sounds at right base anteriorly were more audible than at left. Breath sounds more audible at left apex than at right apex. At the end of an hour breath sounds were more audible front and back at left apex.
13. *Subject on right side:*
    The subject was noted as breathing more decidedly with diaphragm than the other subjects. At the beginning scarcely any breath sounds could be heard at the right apex. At this time the vesicular murmur was heard more markedly on the right side opposite the eighth dorsal spine. The breath sounds in front were a little more audible on the left side.
14. *Subject on right side:*
    The breath sounds were very faint over both sides but less audible over recumbent side. The percussion note was hyperresonant over left side, especially over lower part of chest. The vocal fremitus definitely increased over dependent side, more decided in front.

CONCLUSIONS

1. In all subjects studied the heart and mediastinum became displaced toward the chest wall of the dependent side.

2. In most subjects, but not in all, the diaphragm on the dependent side at first increased its excursion. In all cases this diaphragm, forced up by the abdominal viscera, held a relatively higher position than that of the upper half.

3. The preliminary increase of diaphragm excursion on the dependent side was associated with an increase in the vesicular murmur at the base on that side.

4. At the end of from thirty to sixty minutes the increase in diaphragm excursion and intensity of basal breath sounds had subsided. The diaphragm movement of the two sides may be equal or reversed.

5. In general the breath sounds at the apex are less audible on the recumbent side.

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THE INFLUENCE OF MILD ALLERGIC VASOMOTOR RHINITIS ON PULMONARY TUBERCULOSIS

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The harmful effects of severe vasomotor rhinitis and bronchial asthma on pulmonary tuberculosis are, of course, perfectly comprehensible. The writer has seen, as an extreme instance, one case of spontaneous pneumothorax resulting from the violent sneezing efforts of a patient with severe hay fever (1). Such typical, usually severe, seasonal types of hay fever are so obvious, and their diagnosis and correction are now so well understood, that a discussion of this type of annoying complication is well nigh superfluous.

However, my experience recently has brought me into contact with this complication in a less obvious form which I have not as yet seen mentioned in tuberculosis literature, and which seems to me decidedly well worth notice.

During a study of a series of tuberculosis cases, I attempted to attack the mixed infection problem by what seemed to me the most logical route, namely, its elimination at its source by attention to chronic nasopharyngeal infections by whatever means were deemed essential by a competent nose and throat specialist. Acting along this line, a number of cases were beneficially operated on at my suggestion, and have been reported by Dr. E. M. Sykes (2).

Still, it was noticed that in certain other cases nasal operations did not produce the desired results. Chronic nasal discharge, with both anterior and posterior drip of a mucoid character, persisted indefinitely in spite of operative and local treatment. Such patients, with reference to their nasal condition, as a rule complained merely of susceptibility to frequent colds, their catarrhal annoyance, while present, being on the whole of slight degree. In practically none of them was an unusual amount of sneezing or definite eye or noise symptoms present to indicate obvious vasomotor rhinitis.

The following cases are typical:

Case 1: Mrs. H. S., age 30, married, first seen October 9, 1922, gave a history of treatment for active pulmonary tuberculosis lasting one year. *Involvement:* upper lobe right lung, not extensive, sputum positive, clinical symptoms slight. She was seen during a recurrence of cough after several months of exercise. An acute coryza had been present for ten days, and she gave a history of frequent colds. Hay fever or asthma was denied, and she gave no history of unusual sneezing attacks. Nasal discharge persisted in spite of months of local nose treatment, confirming the history of its past persistence with other colds, all tending to increase cough and expectoration. Cough did not yield to rest cure.

On December 22, the possibility of allergy was considered in this case, and positive intracutaneous reactions were secured by the usual tests to the ragweeds (++ to +++), grasses (++++) and feathers (++++). Feathers were removed from her environment, and preseasonal immunization with grass-pollen extract carried to the point of elimination of the positive skin reaction (final dose 0.3 cc. of 1 to 100 solution).

The nasal symptoms cleared up within a few days after the removal of feather pillows, followed by a rapid reduction and final disappearance of cough. When last seen in September, 1923, nine months later, there had been a single "cold" in March, 1923, undoubtedly infectious in origin, and none since, and for the past six months absolutely no nasal symptoms.

Elimination of a hitherto unsuspected allergic vasomotor rhinitis of minor degree swung the balance in this case at once to an easy arrestment.

Case 2: C. A. N., clergyman, age 35, was first seen January 29, 1923, with a history of chronic fibroid pulmonary tuberculosis extending over a number of years. He was a typical moderately advanced, bilateral, cavity case with positive sputum, and moderate clinical symptoms. It was almost impossible to keep open the windows in the room of this patient, as every draft, as he put it, brought on a cold. Sneezing was almost daily but slight. He had a slight nasal discharge, but no eye or nose symptoms indicative of typical hay fever. He had considered himself in the past slightly bothered by certain pollens, but the season of the year and his environment ruled out any pollen influences. After a sneezing spell of no excessive duration or severity, followed by a prolonged, severe pulmonary hemorrhage that required artificial pneumothorax for its control, the possibly decided influence of this otherwise trifling annoyance was obvious, and a search instituted for its cause. Intracutaneous tests revealed a positive reaction to feathers (+++ to ++++), wool (+++), ragweed (+ to ++) and grasses (++).

Feather pillows were removed from his room, and wool bedding and garment contact eliminated as far as possible. Sneezing stopped within a day or two and has not recurred for the past two months, the nose is entirely comfortable

and without discharge, and drafts are tolerated perfectly well without the previous "colds." In this case also, the sneezing and nose symptoms had never existed to the degree to arouse even a suspicion of allergic rhinitis.

The writer has seen a number of cases of chronic, annually recurring hay fever due to feather pillows and wool. Bronchial asthma due to these antigens has, of course, long been recognized. I have also encountered about a dozen tuberculosis cases of the type of vasomotor rhinitis described, in which the hypersensitiveness was not excessive and the local nasal response was so slight as to cause the overlooking of its true nature. Symptoms of discomfort in these cases are mild, inconspicuous and easily overlooked, consisting of moderate mucoid discharge, with or without slight occasional sneezing attacks. Local nose examination fails to reveal the usual pale, edematous mucous-membrane appearance typical of vasomotor rhinitis. In fact, the nasal picture ordinarily closely approaches the normal. Definite complicating infectious sinusitis may or may not be present, and practically none of the cases of this type yield to local nasal treatment, operative or otherwise. Attention to the antigenic factors involved, by reducing cough, has in a number of these cases led to the clinical betterment of the tuberculous process that previously had not improved as expected.

I believe these cases to be more numerous than is commonly supposed. The usual skin test response in these cases is to feathers alone or to feathers and wool. Also, most of them feel that their nasal discomfort has been increased since the inception of the ordinary tuberculosis rest cure regimen. This is naturally to be expected, since, whereas a previous feather pillow-wool garment contact existed only eight hours a day, the rest cure necessarily increases this contact, at times to twenty-four hours a day, at least in regard to feather pillows, producing symptoms where none had previously existed. It is my custom now to do these skin tests in every tuberculosis case with chronic nasal discharge.

Some of our chronic digestive disturbances in tuberculosis practice may owe their etiology in the same way to increased egg or milk consumption. However, I feel that if proper attention is given to the question of the possibility of the existence of allergic factors in one form or another in our tuberculosis cases, and especially if the minor degrees of unobtrusive vasomotor rhinitis be tested for and recognized as such, fewer unnecessary nasal operations will be done in our tuberculosis cases, their arrestment will be hastened by the removal of another cough-producing influence, and an annoying and possibly dangerous complication obviated.

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SERUM CALCIUM IN SURGICAL TUBERCULOSIS[1]

OTAKAR BARKUS

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The calcium concentration of human serum has been determined by previous workers, and a remarkable constancy in normal, as well as diseased, man ascertained. This statement, however, is based on studies involving a few cases only. Some authors report data collected from a great variety of pathological conditions, but again only a few cases of each disease represented are given. It appeared, therefore, worth while to determine the calcium concentration of human serum in a series of 80 cases, all affected with severe bone lesions, for one may easily expect changes in the normal $\frac{\text{Na. K.}}{\text{Ca.. Mg..}}$ equilibrium, in a case in which large areas of bone and cartilage are being destroyed rapidly or in disease accompanied by pronounced proliferative bone growth. The cases selected were accordingly classified, as to the type of lesion, into destructive, destructive-proliferative (designating a process in which destruction prevails), proliferative-destructive (designating proliferation prevailing), proliferative and atrophic, the causative microörganism in the vast majority being the tubercle bacillus although the number under *proliferative-destructive* includes 3 cases of osteomyelitis and 1 of Legg's disease. The blood was drawn by the ward surgeon, two hours after a meal, no anticoagulant was used, and the determination was made according to Tisdall on the native serum. The figures in the protocol attached are mean values of at least two separate determinations.

Protocol

GROUP	TYPE OF LESION	AGE		TOTAL	CALCIUM CONCENTRATION RANGING		AVERAGE MGM. PER 100 CC.
		From	To		From	To	
1	Destructive	3	37	38	8.8	12.95	10.67
2	Destructive-proliferative	5	31	10	9.8	12.0	10.74
3	Proliferative-destructive	6	34	24	9.2	13.9	10.83
4	Proliferative	9	23	4	8.65	11.2	10.16
5	Atrophic	12	32	3	8.82	9.0	8.94
6	Destructive-atrophic	2		1			10.2

[1] From the Department of Research of the J. N. Adam Memorial Hospital, Perrysburg, New York, John H. Pryor, Medical Director, Horace LoGrasso, Superintendent.

The calcium is slightly increased in groups 1, 2 and 3, yet not to the extent reported by Stheeman (1) who claims that a marked destructive process should naturally be followed by an appreciable rise of the calcium level. This is, however, not the case. Group 4 shows normal calcium values, but a lower average when compared with the destructive types of groups 1 and 3. A definite diminution was observed in group 5, the three cases representing atrophy of both lower extremities, atrophy of upper right and lower left extremities, and general atrophy (tuberculous lesion of the spine, cervical region). Whether this low calcium concentration is due to disturbances of the mineral or of the nitrogen metabolism will be the object of further investigation.

I wish to express my heartiest thanks to Dr. R. P. Schwartz for his active support and coöperation.

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THE SPREAD OF TUBERCULOUS INFECTION IN THE BODY[1,2]

ALLEN K. KRAUSE

Tuberculosis is a conspicuous example of a metastasizing infection. It spreads by concentric growth or direct extension of foci; or by short excursions of bacilli along lymphatics or by their lymphatic passage over greater distances; or by venous or arterial transference; or by conveyance along visceral ducts or channels, as by bronchi, ureter and intestines.

The lymph flows normally in only one direction, that is, always centralward from more peripheral places. While much has been said about retrograde lymphatic infection, that is, a transport of germs against the lymph stream, it is difficult to accept this as a mode of spread under normal anatomic and physiological conditions. It is conceivable, and highly probable, that when a relatively sluggish current like that of the lymph undergoes stasis somewhere, through blocking or obstruction at a more central point, infection settling here might proceed peripheralward by a successive implantation of foci, and thus by continuity run backward against the direction of lymph flow. We may even think that after such a chain of tubercles had thus been laid down along a lymphatic the earlier and more central members of the series might heal and disappear, while the outer ones remained; and thus there would result an uninvolved length of a lymphatic to give the false appearance of a retrograde transmission of infection. By real retrograde infection we understand a very different condition from a continuously successive seeding peripheralward along lymphatics, in which the flow has been slowed or stopped. We must think of it as a central to peripheral passage of bacilli that is uninterrupted for measurable distances and leaves intervening portions of lymphatics free from infection. If this actually happens it must take place counter to the direction of flow of the stream and on past

[1] Part of an address delivered January 16, 1924, before the Bronx County Medical Society, under the auspices of the Bronx County Medical Society and the New York Tuberculosis Association.

[2] From the Kenneth Dows Tuberculosis Research Fund of the Medical Clinic of the Johns Hopkins Hospital and University.

valves that ensure the proper direction of flow all along the channel; and nothing short of scientific demonstration of the occurrence, under conditions of velocity and pressure that obtain in the living body, can lead one to believe in its possibility. To find foreign particles or germs or foci of infection in places that lymphatically are peripheral to the field of experimental inoculation is, of itself, not enough to prove their retrograde lymphatic conveyance.

The lymphatics with their centripetal flow are, in a sense, a part of the venous system and carry to the latter all particles that have proceeded far enough from any peripheral point to reach the great central lymphatic trunks. Germs that get into veins from foci anywhere in the body except the lungs will be transported to the lungs; those that attain the pulmonary veins will go to the heart and be thence distributed arterially to the rest of the body. This is quite likely much the most common course of arterial metastasis, and a first clinical manifestation of tuberculosis in structures like a joint, to which infection must have been brought by the blood, the arterial blood, raises a strong presumption that it came to the joint from older concealed and unsuspected foci in the lungs: such is the presumption, yet there is always the possibility of its origin in some focus even more remote; from, say, one in a lymph node, from which germs might go by the veins, heart and pulmonary artery to the lungs, and then on through the lungs, and back again to heart and by the arterial system to the joint; or even from still more distant foci, as perhaps from one in a lymph node into lymphatic trunk and thence to veins, lungs and further to the body at large.

We may not ignore the possibility of escape of bacilli from foci apposed to arteries into the latter and the consequent transport of infection to limited, fanshaped fields supplied by the terminals of such arteries. Yet this must be a relatively uncommon method of metastasis, and we are not likely to go wrong often if we look upon arterial-borne infection as having come from the lungs, with always the possibility that it might have originated in some structure on the lymphatic or venous side of the circulation and have passed through the lungs. When, therefore, bones and joints or kidney or central nervous system without generalized infection or eye or even skin exhibit the first signs of tuberculosis in the body it is the lungs which one should search for the hidden foci of origin.

While the lungs, in their central position, may thus be the fount of isolated tubercle for the body at large, they are also the destination and receiving station for infection that becomes detached from foci anywhere

else in the body and is carried to lymphatics and veins. To them can go bacilli from lymph nodes and all other structures and organs of the body. What proportion of all such material sticks in the lungs and sets up new foci there must no doubt remain a subject for rather futile speculation and dispute. But there can be little doubt that it is large; and that which does not settle down there passes on into the arterial system for dispersive distribution.

It is important, therefore, to remember that, if infection is established in the body and it becomes set in motion by the circulation, the chances of new focalization are (1) if the tubercle in question is in the lungs, then to the rest of the body and (2) if it is in places other than the lungs, then to the lungs.

In spreading infection by visceral duct no organs begin to compare with the lungs in capacity for mischief. After foci communicate with bronchi the way is open for their contents to be carried to all parts of the same lung, to the opposite lung, to the larynx and, in a more roundabout way, to the intestines.

Only a moment's attention to circumstances, such as the above, is enough to indicate why, on the one hand, the lung is so frequently involved in human infection, and why, in general, its involvement far overshadows that of any other part of the body in importance and in seriousness. To explain its immoderate frequency of clinical infection we do not have to call upon such highly hypothetical contingencies as that it is by nature a place of lesser resistance—a circumstance that has no shadow of demonstrated fact to support it; it is far more likely that outspoken infection of the lung occurs so often because of the lung's extraordinarily favorable position to receive infection—not once, but again and again. It begins by being open to what would seem like a most fertile method of infection from the outside, that is, by the inhalation of air-borne germs; and, in addition, it is the converging depot of all bacilli that make the journey centralward by lymph or blood from foci anywhere in the body. It is again unique that it may even be in danger from its own lymph nodes; for, if these become tuberculous and discharge their contents, they scatter infection through the very organs which they drain. At the same time infection of the lung, with everything else equal, must also be more menacing than that of any other organ, as it possesses the capacity to throw abroad infection to every other part of the body by the blood and to the upper respiratory and digestive tracts by the bronchi.

Even this necessarily incomplete and summary account of metastasis will suggest how important in contributing to the event and determining the issue in any particular case must be the localization of significant infections and the channels open to their further migration. In actual practice it *may* be easy to follow the march of infection, especially after it has once thrown out signs of its presence; but much more often the sequence of events is anything but plain; and even though focus after focus may show itself in so orderly and successive a way that the course of infection seems laid bare it may be doubted whether available methods of observation of the human being will disclose more than the cruder and more marked evidences or outlines of the infection. What come within our recognition as tubercle in the patient are, first, foci that have progressed to a stage and are in a location to disturb function and, second, whatever other tuberculous changes may be present anywhere else large enough to be detected, yet not perhaps setting up symptoms. We notice one or several separate processes, isolated and perhaps far from one another; and, after coming upon essentially the same disposition in patient after patient we incline to concepts of tuberculosis that would consider it as originating as a strictly localized infection and generally progressing through the outcropping of new localized infections from bacilli that have come from foci already present. We think of a certain number of germs as gaining access to the body and then, more or less *en masse*, settling down in the tissues at one point that may be a variable distance from the portal of entry. We then visualize the totality of these germs of first infection as giving rise to a first focus and this first focus, for a time at least, as representing the single spot of infection within the body and the source of whatever tubercle may appear in the body later. And we speak of the immunity which this solitary first focus has conferred, and tell how, even though later contact with outside germs may be struck, no harm, no "take," will result unless the numbers of bacilli are too large for the immunity to cope with. Few of us, it would seem, think of the possibility of a more general distribution of infection as perhaps *the mode* of tuberculosis; of bacilli nesting in many places throughout the body, once entrance is made, and causing only minimal or microscopic, in other words, unnoticed changes in many tissues, with only a single visible focus, or a few here and there, to indicate infection; with, maybe, a rather free and frequent moving about of small numbers of germs along the various avenues of dissemination and a consequent repeated new focalization that is widespread, the early focus of relatively

many bacilli and of native tissue reaction remaining the only visible process and the numerous minute foci of few bacilli remaining concealed with their growth kept in abeyance by the immunity of the body as long as this holds.

Yet there are some more or less well known features of tuberculous infection to suggest that *characteristically* it takes on a multiplicity rather than a singleness of localization; that even from the beginning there is a relatively general distribution of bacilli rather than their concentration at one place; that its evolution is analogous, not so much to that of cancer which, presumably beginning from "aberrant" cells at a single point, in time gets to propagating grafts to other locations, as to that of syphilis with its microörganisms well distributed throughout the body by the time its focus of inoculation comes to light, with its subsequent variably active phase of still further general distribution, and with its later characteristics of single or few visible (clinical) foci in a body that harbors its germs in many places. Even though its clinical appearances are preponderantly local or isolated, we have grown to look upon syphilis as characteristically a general infection—as a "saturating" one, if you will allow the term. Tuberculosis we have regarded just oppositely;—as eminently focal, with every part of the body not affected with visible tubercle as uninvolved by the infection and unimpaired. There is no doubt that if syphilis did not in so many cases go through its well marked and rapid secondary stage, with evidences of active dissemination plain, we would class it with tuberculosis as a focal and focally metastasizing infection; we would then have only the inoculation focus with its early tributary lymphatic involvement and the much later circumscribed foci of gummata or sclerosing changes to guide us. In tuberculosis, as it ordinarily develops, we lack the sharp second stage that would at once suggest its resemblance to syphilis; yet we do see something not much different if direct inoculations, fundamentally similar to those that originate syphilis, are made; as, for instance, after wound infections in infants. Moreover, close examination of experimental infection, correlated with scattered clinical observations, indicates further that tuberculosis has more elements of being a general infection than is superficially apparent or is generally recognized.

The number of cases of osseoarticular and genitourinary tuberculosis that develop in persons who have never before shown evidences of the disease, is in the aggregate large. We must believe that in practically every such case the infection of first clinical importance came to the

affected place by the blood; in a person, moreover, who has had an unsuspected though measurable focus somewhere. This means that there has been a bacteremia of tubercle bacilli; and, even though we take into the reckoning only those patients with primary clinical tuberculosis of "shut-in" organs, we must conclude that bacteremia of tubercle bacilli is relatively common even in people with what we would call minimal infection,—at any rate, with infection that had been so well taken care of previously that the "seeding" focus had not extended far and had not sent over to the body material enough to poison it. Other blood-borne forms, like meningitis, tuberculids, kerato-conjunctivitis and generalized miliary tuberculosis, in previously healthy people, may not make up as large a part of practice as primary kidney and bone disease; yet, taken together, they are met with in general hospitals as frequently as pernicious anemia or even gastric ulcer.

Such clinical experience, while it may not prove that a more or less general distribution of bacilli is the rule after tuberculous infection is established, is first class evidence that it is quite common. And one becomes the more inclined to an hypothesis of generalization after considering strong probabilities like the following: (1) that when primary kidney or bone tuberculosis does arise it is not likely that they are the result of the only germs that have been carried around in the blood—the chances are rather that bacilli have gone to several or many places, and that isolated disease in one place has been brought into being by local and general factors that favored a progression of the infection there; (2) that an actual spreading of bacilli by the blood in tuberculous infection in general is much more frequent than the number of cases that come to clinical appreciation; for there is no more certain fact in tuberculosis than that the number of infections of any structure is many times the number of symptomatic foci, or that clinical disease of an organ develops once for every five or ten or fifty times (we know no more than that it is many) that tubercle bacilli lodge there.

In any speculation on the fundamental character of tuberculous infection more weight than is usual should be given the fact that demonstrable infection occurs most frequently in human beings in a place where outspoken disease is relatively uncommon,—in the very place too that is the central point of reception of infection from every part of the body. A systematic and complete search for tubercle bacilli in the human body is a scientific impossibility; for it would involve the serial sectioning of every structure, or the inoculation into animals of each *in toto*, or both.

Yet, from comparatively rough observation, there has resulted a general accord that the lymph nodes at the root of the lungs, the tracheobronchials, harbor tubercle more often than any other part of the body, and there is no dispute about clinical disease of these lymph nodes *alone* being unusual. Tubercle, of course, occurs in these nodes whenever it exists in the lungs, for the nodes drain the lungs. But it is also present here when it is not to be found in the lungs,—when it is in other parts of the body or when cursory examination will not reveal it anywhere else. The increasing use of the X-ray in examination of the chest is teaching us, more and more, how enormously common are mediastinal changes. "Enlargement of the mediastinum" or "chronic mediastinitis" runs through the X-ray reports, especially those of children's examinations, like a song; with a monotony that makes one wonder whether mediastinal changes are not the norm for the young. In the ordinary child, with its ordinary several years of childhood infections to surmount, we may believe that a residuum shows for a time at the lung hilum and that density changes there are not necessarily the signs of tubercle. But the definite X-ray alterations at the lung root that accompany affections like tuberculous cervical adenitis, with and without symptoms, are frequently too impressive to permit of any other opinion than that tuberculous infection is also then present in the tracheobronchial nodes. Not long after the discovery of the tubercle bacillus Pizzini, by animal inoculation, found virulent tubercle bacilli in the morphologically intact tracheobronchial lymph nodes of almost half of the cadavers of forty adults who had died of accident or acute disease; of course, "morphologically intact" means no more than that ordinary gross and microscopic examination disclosed no tubercle, and does not rule out that pathological reaction was present somewhere in the nodes.

While, therefore, we are far from saying that mediastinal changes, X-ray or otherwise, invariably mean tuberculous infection of the hilum nodes, we do have some warrant on clinical grounds to support the opinion that they may be frequently involved when infection other than pulmonary exists, which would then mean a transference of infection far from a more original focalization. Theoretically, an infection of these nodes could be brought to them by their artery of supply from elsewhere in the body; but enough is known to make certain that in nearly every case the infection is much more indirect that this;—that it has resulted from bacilli brought to the lungs either from without by the inspired air or from an extrapulmonary focus by the blood, and from the

lungs the bacilli are carried lymphatically to the root nodes. This latter combination of routes carries infection again and again from a more primary tuberculosis of the cervical lymph nodes to the tracheobronchials. Then, in some instances, when we carry the examination further back, and section enucleated normal-appearing tonsils, or inoculate these into animals, we find infection, still more primary, in the tonsils; so that in a patient who clinically suffers only from tuberculosis of the neck nodes we have three separate centres of focalization in the body; that is, tonsils, neck nodes and tracheobronchial nodes. And then still closer examination may reveal a spot in the lungs, one that has never produced symptoms; and, besides, there may occur a transient skin eruption, too slight symptomatically to appear of much significance and its real nature not understood unless a physician, who is on the alert for tuberculids and who has at hand other information like X-ray plates of the chest and histological sections of the tonsils, observes the patient. The tuberculids, set up by bacilli that have been carried far from central foci by the arteries and spread widely, are in themselves good evidence of how generalized tuberculous infection may be and yet hardly produce illness.

For the case that I have been putting together piecemeal for you is not a hypothetical and ideal one. It occurs often enough in practice, particularly in children, in whom we must assume that the original infection from without must have been received not long before, and that this casting out, as it were, of several lines of infection represents an early generalization, with few or no symptoms,—a quiet preparation of a setting that may blaze up somewhere many years later. In our own hospital it is not the rarest of events to see a child, physically under par perhaps yet not in particularly poor health, with determinable infection of the neck and lung hilum nodes, the conjunctiva and cornea, the skin, and perhaps the lungs; and to have the few symptoms subside after a time. Many may develop clinical infection in still other locations, as in the bones and subcutaneous tissues and other superficial lymph nodes than the neck, and also make good recoveries. These healing though widely distributed infections need by no means be of bovine-bacillus origin, as has been suggested; many occur in children who live with relatives with far advanced pulmonary tuberculosis, of unquestionably human-bacillus etiology, and by isolating the bacillus from superficial foci I have satisfied myself of the human-type infection of some of these cases.

We are accustomed to think of generalized tuberculous infection only in terms of its extreme clinical form, generalized miliary tuberculosis. The point I wish to make is that clinically there is a not uncommon generalization of infection of much more benign type; and that, again mindful of the law that tuberculous infection may always be assumed to be more frequent than clinical manifestations disclose, we may be permitted the deduction that a generalization of infection is an ordinary event—though please grasp the implication that it is more likely to be of slight or minor degree and asymptomatic, inasmuch as the bacilli concerned in setting up the several foci are relatively few. And it is, moreover, significant that available clinical evidence points to a greater tendency to generalization, with few or no symptoms, in childhood, that is, comparatively early in the natural history of the infection. Here then an analogy to syphilitic infection becomes plainer.

Any opinion formed from careful animal experimentation alone might question whether tuberculous infection of a susceptible animal were ever, at any time, the strictly localized affair that we commonly think of. A number of years ago I first became impressed by the fact that tubercle bacilli of slight virulence, if put into the guinea pig subcutaneously, would spread throughout the body, although they set up visible tubercle in only a few places. Since an infection made subcutaneously will begin by the lymph channels, there would result a fairly prompt involvement of the lymph nodes tributary to the site of inoculation, and to superficial observation this was all that occurred, as such an animal lived years in good health and with nutrition and reproductive capacity unimpaired. The viscera remained free from noticeable infection, and slowly the process in the regional lymph nodes would become well sclerosed and shut in; reminding one, in fact, of the type of infection that we are accustomed to find in human beings who, though with tubercle, have never given evidences of it; that is, a solitary well-invested focus somewhere in relation to a portal of entry.

But, after a while, closer examination of these animals revealed that the tracheobronchial lymph nodes were also invariably involved. They were enlarged and indubitably infected. This circumstance could mean nothing else than that bacilli had made the complete journey from the groin, lymphatically to the veins and then on to the lungs, and, after having been carried out of the blood vessels of the lungs, lymphatically again to the hilum lymph nodes; and I had to give up my older idea that in guinea pigs, after a subcutaneous entry, germs of low virulence, pre-

sumably therefore of slender parasitism, were arrested at or near the point of inoculation by the new anatomic barrier of tubercle and were thus hindered from going further and exerting their effects in other parts of the body. They did indeed spread far from the spot of first infection and probably produced some minute reaction at many places; but it was in a place of converging avenues of infection, like the tracheobronchial lymph nodes, a central depot where infection could accumulate, that noticeable changes, besides those in the immediately affected lymph nodes, took place.

I then studied systematically the manner and rate of distribution of living, virulent tubercle bacilli in the guinea-pig body given a single inoculation beneath the skin. Dispersion of bacilli was amazingly rapid: long before tubercle became noticeable at the site of inoculation living bacilli were recoverable from practically every part of the body: within four days or less they could be proved, by the inoculation of tissues into new guinea pigs, to have made the transit of the body and to have settled out into tissues at many places. And this fixation took place weeks before visible changes would appear in some organs; indeed, it would take place in tissues that would later show no changes.

My associate, Doctor H. S. Willis, has since investigated, still more minutely, the rate of mobilization of living tubercle bacilli within the first few days after their inoculation into guinea pigs. He has made his inoculations *into* (not beneath) the skin of the side, at a point from which, we know by experience, the germs will proceed to the inguinal nodes and then pass on to the interior of the body. He has then excised the fields of inoculation and, after dressing the surgical wound, simply put the animals back in their cages and allowed them to live, observing carefully meanwhile whether infection would appear in the body and how soon it would become manifest and how far it would progress. He performed his excisions at first almost hourly for twenty-four hours after inoculation and then daily. He has thus found that by the end of the first hour after infection the bacilli have proceeded beyond the half-inch or so that comprised the radius of his field of enucleated skin; for all animals with infection site cut out, from one hour after infection on, have gone on to generalized tuberculosis.

Now his places of infection drain lymphatically, as has been said, to the inguinal nodes. These lie about two or three inches away from the point where inoculations were made and study of them promised a method of determining how rapidly the bacilli traversed this space.

Doctor Willis accordingly inoculated other series of guinea pigs *intracutaneously;* but, instead of excising the sites of these inoculations, he allowed the latter to remain, and enucleated their inguinal nodes, hour by hour and later day by day, and inoculated new guinea pigs with these nodes. He found that such nodes would not produce tuberculosis in the new animals if they were removed earlier than twenty-four hours after infection of the skin, but that nodes taken out later than twenty-four hours would set up infection regularly. In other words, during the first day after infection the inoculated bacilli were somewhere between the site of infection and the draining lymph nodes two or three inches away; and by the end of twenty-four hours they had traversed this space.[3]

The orderly and step-like progression of tubercle in guinea pigs, after a single virulent inoculation, certainly would not suggest so rapid and "far-flung" a disposition of germs from the point of entry; and Doctor Willis and myself were rather astonished at the results of our efforts to keep track of the spread of the bacilli. As has often been described, the course of guinea-pig infection, after subcutaneous inoculation in the groin or intracutaneous inoculation in the side, evolves with fair uniformity as follows: Toward the end of the second week noticeable swelling and induration of the inguinal lymph nodes of the same side appears; a few days later, enlargement and textural changes of the next centralward larger lymph nodes of the same side, the so called iliacs, that lie retroperitoneally along the great abdominal vessels; in the fourth week, on the average, minute discrete nodules in the spleen, and then also, or perhaps a little earlier, swelling and hardening and whitening of the lymph nodes at the root of the lung; and from now on the process in the spleen advances especially, while foci come to light in the lungs and liver, and, all viscera becoming continually more involved, the animals die from six to eight or ten weeks after ordinary virulent infection. Such a sequence of events has caused most of us, I think, to believe that the successively appearing foci, arising in structures situated serially, as it were, along avenues of transport, originated from bacilli sent centralward from foci established previously in the more peripheral structures of the chain. Moreover, we also imagined that, in its earliest development, infection proceeded haltingly, by successive short journeys from older to new locations, with shorter or longer periods of arrest of transport in each new place. I still believe that this interrupted manner of progression takes

[3] These studies will be published in a later issue of the AMERICAN REVIEW OF TUBERCULOSIS.

place in guinea pigs, but it has become plain to us that after infection there occurs, in addition, an almost immediate carriage of some bacilli to points at a distance from the place of entry and, if the germs of infection are numerous enough, to many widely separated points far in the interior of the body. And we have every reason to think that more or less permanent foci, capable of further development, may originate from these bacilli of early distribution.

The guinea pig has lent itself admirably to the study of specific immunity to tuberculosis. In from six to ten weeks after a single virulent infection a guinea pig will die with tubercle well marked in spleen, lungs and liver especially. If, however, guinea pigs are first given single infections of low virulence, they become highly resistant to later single virulent reinfections that will affect originally nontuberculous animals in the way mentioned. These immunized animals will remain in complete health and, if slaughtered two or three months after virulent reinfection, will exhibit few, if any, visible foci in their viscera—to the naked eye, these internal organs, as often as not, appear completely normal.

This circumstance has led us to believe that, in some way or other (perhaps with the coöperation of the allergic reaction), the virulent bacilli of reinfection are halted and, maybe, largely destroyed at their point of entry in the immune animal, and that further progression of infection does not take place because of their failure to get further or far into the body.

But recent experiments in our laboratory have shown us that a complete or decisive check to bacilli *in situ* does not take place in such apparently immune animals. If, for reinfection, we use the same doses of virulent bacilli that will produce progressive tuberculosis in nonimmune guinea pigs, with death in two or three months and, within the same time, no visible visceral tubercle in the reinfected animals, we find nevertheless that in the latter also there occurs regularly a dissemination of virulent bacilli throughout the body. For weeks and months after virulent reinfection the tissues and organs of the immunes, though not showing gross tubercle, will, if inoculated into new normal guinea pigs, produce tuberculosis in the latter in a way that allows no idea that residence in the immune animals has reduced the virulence of the bacilli.

Nevertheless, there are well marked differences between nonimmunes and immunes as concerns the rate of distribution of bacilli and, no doubt, their numbers as well. In the immune the germs reach given internal parts of the body several days to two or three weeks later than in the non-

immunes, and for a month, at least, after infection there are always fewer virulent bacilli at any place in the immune. And we have found too that, while for months virulent reinfection may be held in check in the immunes, so that we may see no organic involvement in them, it sooner or later comes to the front if the animals are allowed to live long enough. All these guinea pigs, that were apparently completely resistant to our dosages three months after reinfection, die of tuberculosis by the end of a year or more, with their organs extensively involved.[4]

This lengthy account of the metastasis of tuberculous infection may seem unpardonably tiresome in a general address of this kind. My apology will be that we cannot understand tuberculosis biologically or medically unless we know how infection takes hold of the body—what are really its relations with tissues individually and the body as a coördinated economy—and how it goes from place to place within the body. Our knowledge in both respects is admittedly imperfect and faulty; the necessarily obscure act of human infection—without possibility of marking time and manner, as in syphilis—only too often, indeed, without circumstantiality of incident; the characteristic leisurely evolution after bacilli make entry, and often peculiarly unobtrusive manner of reaching out from place to place; the catholicity of affinity for animal tissues and adaptability to every avenue of transport; the undoubted capacity to persist without tell-tale anatomic or physiological disturbance; the confusing new attributes that it endows the body with;—all help to make tuberculous infection a subject of extraordinary complexity and indefiniteness. But, out of a multitude of manifestations in human subjects and animals of experiment, we would build up a working hypothesis of the nature of tuberculous infection in man. It would proceed from the assumption that in our present society the opportunities of contact with living tubercle bacilli are almost boundless and endless. It would consider as a fact that in these contacts every gradation of quantity and quality of bacilli, every relation of time and every possible mode and place of entry of infection entered into the reception of bacilli; that in any one infection bacilli may be received singly or in enormous numbers and as germs of slight virulence and viability or of the highest tenacity and parasitism; that germs from without may be received once in a lifetime, or several times with longer or shorter intervals between, or oft-repeated and almost continuously throughout long or short periods; that coming

[4] These studies will be published in a later issue of the AMERICAN REVIEW OF TUBERCULOSIS.

in by mouth, nose or skin, but almost always by mouth or nose, bacilli actually penetrate the body at any point along the respiratory or digestive tract; and that every one of these variable circumstances molds, in its way, the nature and course of infection that are to result.

When, therefore, single or a very few bacilli settle at a point, to form a focus of first infection, this hypothesis would assume that for a time, maybe rather short, infection may be localized to one spot; yet that, if any moderate or considerable increase of germs takes place, these are moved to other parts of the body, and their mobilization is the more readily and widely affected as this occurs before allergy is established or before it is high; for allergy operates to fix bacilli where they lodge or greatly retard their spread. If first infection involves the penetration of numerous bacilli there is a rapid and comparatively widespread distribution of germs, so that by the time allergy gets under way several or numerous focalizations, each no doubt of comparatively few germs except the initial depot, have been established in the body. Immunity, never complete, may not be conceived of ordinarily as *preventing* reinfection; it abates in varying degree the natural invasiveness of the latter, retards its inherent power to spread, modifies (as compared with first infection) the resulting anatomic reaction. By and large, tuberculous infection is to be thought of as a condition of bacilli at several or many places and frequently moving to new locations, rather than one of bacilli only in single visible foci or in several foci that have resulted *seriatim* and exclusively from an earlier one along an avenue of transport: at any rate, the number of foci demonstrable anatomically is always greater than the number appreciable clinically, and the number of places where bacilli reside always greater than the number of visible foci. Size and character of individual foci are determined by the number of bacilli that originally settle at the place, by the number that may continue to come to the place, by the allergic power of the tissues involved at any and every time of focalization, as well as at all periods in between, and by the physiological condition of the body and tissues, in as far as functional changes affect tubercle within the body. Such, in very broad outline, are the outstanding variables which through their almost infinite capacity of reciprocal interaction go into the making of the extremely complicated and multiform evolution of tuberculous infection.

THE CONCENTRATION OF BACTERIA, INCLUDING TUBERCLE BACILLI, BY THE USE OF ALUMINIUM HYDROXIDE CREAM[1]

CLARENCE C. SAELHOF

Suggestions for the concentration of bacteria in quantities of fluid have been advanced, more particularly by the use of kaolin, colloidal iron and other substances. It was thought that perhaps by the use of aluminium hydroxide cream a concentration of microörganisms might be effected easily. Aluminium hydroxide cream is made by adding a slight excess of 1 per cent solution of ammonium hydroxide to a 1 per cent solution of ammonium alum at room temperature. The material is then washed by decantation until the wash water shows only the faintest trace of residue on evaporation. It has the ability of removing the smallest amounts of protein material from large volumes of fluid. (*Tracy and Welker, J. Biol. Chem., 1915, xxv, 55. Welker and Marshall, J. Am. Chem. Soc., 1913, xxv, 820.*)

The following experiment was then made: A series of test tubes, each containing 5 cc. of salt solution, was inoculated with a suspension of *Staphylococcus albus* in gradient dilutions. The material in each tube was then divided into equal parts; to one-half was added 5 drops of aluminium cream, vigorously shaken for two minutes and whirled in the centrifuge just sufficiently to throw out the cream. Thin smears were stained by the Gram method. The other half was centrifugated for one-half hour and smears from the sediment stained in a similar manner. Examination revealed 40 to 50 per cent greater number of bacteria per field in the aluminium than in the control smear. Bacteria were observed to the same dilution by both methods. Since the aluminium cream retains the counterstain, it apparently cannot be used with gram-negative microörganisms; however, by constant observation one is able to distinguish the bacteria quite readily, from the stained granules of the cream.

[1] From the John McCormick Institute for Infectious Diseases and the laboratories of the City of Chicago Municipal Tuberculosis Sanitarium.

Samples of tuberculous arachnoid fluid were divided into halves: one portion was treated by the cream method and the other half centrifugated for one-half hour. Thin smears stained by the Ziehl-Neelsen procedure revealed the tubercle bacillus as a red rod against a blue granular background, the number of bacteria per field being slightly greater in the cream than in the untreated slide. In addition, there was a manifest saving of 20 minutes' time for each specimen examined.

Pleural fluid was treated in like manner as the arachnoid fluid with equally as good results.

Tuberculous sputum, treated by the antiformin method, just before its final centrifugation, was divided into equal parts: to one-half was added 5 drops of aluminium cream, the tube was shaken and whirled in the centrifuge sufficiently to throw out the cream, and thin smears were made and stained by appropriate methods. The other half was centrifugated for one-half hour, and smears were made and stained. The results revealed the bacilli per field about 10 per cent greater in number in the cream than in the control slide. Furthermore, there was a saving of 20 minutes in preparation by the new method.

The use of aluminium hydroxide cream affords a simplified and rapid method for the concentration of bacteria in quantities of fluid. Recently, Wile and Kirchner (*Arch. Derm. and Syph., 1923, viii, 831*) used aluminium hydroxide cream as an agglutinative agent for the demonstration of spirochetes in the spinal fluid.

CONCLUSIONS

A method for the rapid concentration of bacteria in fluid medium by the use of aluminium hydroxide cream is presented.

A saving of approximately 20 minutes is made per single specimen examined.

It forms as excellent background for microörganisms which do not take the counterstain of Gram's method.

THE USE OF VOLATILE HYDROCARBONS IN THE CONCENTRATION OF TUBERCLE BACILLI

PAUL M. ANDRUS AND H. EDWARD MACMAHON[1]

We have long recognized the need for improved technique in the demonstration of tubercle bacilli in morbid products.

We have from time to time investigated methods appearing in the literature, but have been disappointed in that concentration was poor and irregular and the staining and, therefore, diagnostic properties of the microörganisms considerably impaired. This is apparently the common experience, as the majority of our leading sanatoria continue to use only the direct-smear method. Thus, Jones (1) has stated, "Neither the antiformin nor autoclave method of sputum examination for the *Bacillus tuberculosis* to any extent surpasses the direct smear;" and again A. H. Caulfeild (2), "Those who prefer to search for the bacillus in treated sputum claim only a slightly higher percentage of positive findings. It is questionable whether the time employed in treating the sputum could not with almost equal advantage be spent with two important features of the direct method," namely, "the selection for spreading and staining of likely particles . . . . and the time and care spent in searching with the microscope."

That revision of our methods of searching for tubercle bacilli is an outstanding need in the field of chest diagnosis is evidenced by the findings in the 182 clinically tuberculous dealt with in this paper. In this group, which is representative of our patients in residence at a given time, 60 per cent of the diagnoses were made in spite of the failure to demonstrate bacilli after repeated examinations by the direct method.

Of interest, as indicating the frequency of bacillary excretion, are the statistics of Lampson (3), who studied the incidence of tuberculous infection among the contacts of open and closed cases, and in nontuberculous families. Thus, of individuals exposed in a household to an open case of tuberculosis for one year, 67 per cent became infected. Of those similarly exposed to cases clinically recognizable but in whose excretions the

[1] Queen Alexandra Sanatorium, London, Ontario.

tubercle bacillus could not be demonstrated (classed as latent and healed), 27.5 per cent became infected as compared with 2.5 per cent in nontuberculous families. Thus, excluding this 2.5 per cent as presumably attributable to outside sources, we have 25 per cent of our so called closed tuberculosis cases who are, in reality, excreting bacilli in sufficient numbers to infect contacts.

Through the kindness of Doctor F. M. Pottenger of Monrovia, California, our attention has been drawn to the merits of the volatile hydrocarbons in removing bacilli from dissolved sputum. This principle, as used by Kinyoun (4) and others, consists of dissolving the material with hypochlorite solution, shaking with ligroin and centrifugating, the bacilli being found in the soapy layer formed between the ligroin and the dissolved material. Krauss and Fleming (5) recommend shaking with saline and gasoline and centrifugating, the bacilli being recovered in the gasoline layer.

Pottenger (6) uses 0.5 per cent solution of caustic soda, immersion in a water bath at 55° to 65°C. to dissolve the material, and shaking in a mechanical shaker with gasoline. The outstanding advantages of this method appear to lie, first, in the use of weak alkali that results in minimal damage to the microörganisms and, second, in the use of the mechanical shaker. The very excellent distribution obtained in this way is, as shown by Pottenger, of equal importance to concentration in the search for microörganisms.

We have modified this latter technique only in the use of a different hydrocarbon and in insisting on fairly rapid centrifugalization. We have felt that in our hands, at least, the results have been very superior to those obtained by other methods.

We have used this technique on the sputum of 200 persons, with a total of over 300 examinations. A second specimen was thus concentrated in over half the cases, uniform agreement between duplicate tests being found. The tests repeated were of course on those presenting the more difficult clinical problems.

Extraordinary care has been taken to prevent contamination from glassware or reagents. Distilled water was used for all solutions; new microscopic slides were invariably used; and glassware was cleaned with caustic solutions and thorough washing. An even distribution of microörganisms on the slides may be considered ample insurance against contamination after the slides are prepared. Typical and well stained acid-fast bacilli have been invariably demonstrated in two slides from

the same specimen before calling them positive. The time of search has averaged 20 minutes with a minimum of 15. Although our routine smears, with which the comparisons in this paper were made, were not searched for this length of time, the multiplicity of examinations, namely, a minimum of 10 and average of 14, would appear to more than compensate for this difference in time of search.

It is of importance that the examiner of the slides had no clinical knowledge regarding the patients represented, and can therefore be fairly considered to have been unprejudiced as to length of search or decision on microörganisms.

The *clinical correlation* has been as follows: A preliminary series of 43 specimens, positive for tubercle bacilli by the direct method, was studied to demonstrate, first, the ability of the technique to invariably show the bacilli in good condition and with serviceable concentration, and secondly for comparison with other methods. This group, varying from very scanty to abundant bacilli, showed in each case acid-fast bacteria in markedly increased numbers, and with good distribution and staining properties.

A second group consisted of 33 persons, whose sputum had been positive by the direct method from 3 months to 3 years previously, with an average of 7 months. These cases averaged 12 negative direct-smear examinations since the last positive finding. Of these, only one failed to show bacilli by concentration. This case had been negative for 10 months by direct smear and was discharged as not requiring treatment.

A third group consisted of 124 persons in whose sputum tubercle bacilli had never been demonstrated. Specimens from these had been negative by the direct method from 10 to 40 times, with an average of 14. Of this group, 18 were classed as nontuberculous, leaving 106 diagnosed tuberculous after intensive clinical study, invariably including stereoscopic roentgenograms.

Thus we have 106 clinically tuberculous persons in whose sputum tubercle bacilli had never been demonstrated after repeated searches. Of this group, 61, or 58 per cent, were found positive by the hydrocarbon concentration technique, a result which would seem to well justify the increased labor and expense involved. It would seem also that this demonstration of bacilli in considerable numbers of "sputum-negative cases," would bear out the quotation in the earlier paragraphs of this article, in regard to the infectivity of "closed cases" of tuberculosis.

Of the 18 persons classed as nontuberculous, we have been forced to change the diagnosis in 5 by the demonstration in each of acid-fast bacilli on three consecutive occasions. These cases were previously diagnosed (1) lung abscess, (2) infectious endocarditis, (3) bronchial asthma, (4) nonspecific chronic bronchitis and (5) gun-shot wound of the chest.

In the remaining 45 tuberculous persons, always negative by direct smear (43 per cent of direct-method negative group), we were unable to demonstrate acid-fast bacilli by concentration, many having second and third examinations.

The types of cases represented by the concentration-positive and negative groups are, however, materially different. Whereas, in the concentration-positive groups practically all had typical parenchymatous tuberculous lesions, in the concentration-negative group only 21, that is, less than half, could be similarly classed. The remainder, although definitely diagnosed clinically tuberculous, had the type of lesions commonly called peribronchial; some, pleural tuberculosis; and others were in the process of being discharged as not requiring further treatment. In other words, a considerable proportion of the positive concentration findings were in those with the more typical parenchymatous lesions.

TECHNIQUE

1. Specimens must be clean and free from food or extraneous matter.

2. The optimum amount is about one ounce, and material should be collected to this end, if necessary, over several days. Scanty and large amounts may, however, be handled.

3. Six-ounce wide-mouth bottles are ideal for the manipulations, using a new cork for each specimen. Glassware must of course be scrupulously clean to eliminate contamination.

4. Two to 4 cc. of 1 per cent solution of carbolic acid are added to the specimen and roughly mixed. This has resulted in uniformly brilliant staining of the bacilli.

5. According to the viscosity of the specimen, one or two volumes of 0.5 per cent solution of caustic soda are added, and immersed in 55° to 65°C. bath until dissolved (usually about one-half hour), and vigorously shaken by hand at 5 to 10 minute intervals. By this technique the specimen becomes homogeneous and relatively transparent. If insoluble particles are present they should be allowed to settle and the supernatant fluid decanted.

6. Cool, and add 3 per cent of chloroform. Shake in mechanical shaker for 20 minutes. Promptly transfer to large centrifuge tubes and centrifugate fairly rapidly for 20 minutes.

7. Remove supernatant fluid completely be means of vacuum suction pump and thoroughly mix sediment with glass or platinum spatula.

8. Smears are made with the entire sediment, preferably one thick and one thin, gently dried, fixed and stained in the usual manner.

DISCUSSION OF TECHNIQUE

While the technique presents no particular difficulties, attention to detail is necessary to ensure finding the bacilli when present.

The solvent: One-half per cent solution of caustic soda gives adequate solution of the material and does not injure the bacilli in two hours at 60°C. One per cent solution does not appear to damage the bacilli under usual conditions, but 2 per cent solution may cause loss of staining properties in half an hour at 60°C. One per cent sodium carbonate solution is a satisfactory substitute. The temperature must not exceed the prescribed limits. We have observed damage to the bacilli in half an hour at 75°C. with the weak alkali. Antiformin and hypochlorite solutions may rapidly damage or destroy the bacilli. The usual mucopurulent specimens are readily dissolved with an equal volume of 0.5 per cent caustic soda solution in one-half hour or less. With heavy purulent specimens it is preferable to increase the volume of alkali rather than prolong the time of solution in the bath.

Centrifugalization: We have demonstrated that concentration is materially less when the centrifuge is not used, even when allowed to stand twenty-four hours. We have been able to demonstrate bacilli in all layers of the specimen when the standing method was used, but never in any but the chloroform layer after rapid centrifugation for twenty minutes.

The hydrocarbon: The advantages of the heavier hydrocarbons (chloroform), which go to the bottom, over the lighter ones which come to the surface, are to us outstanding.

(a) It is practically impossible to remove surface layers cleanly or in their entirety, and free from subnatant fluid. With the heavier hydrocarbon the supernatant fluid may with ease be removed to the last drop with the vacuum suction pump, or with pipette and teat.

(b) The entire sediment (containing practically all the bacilli from the specimen) may be used for smears. The sediment from one ounce of sputum is a satisfactory amount for one thick and one thinner preparation.

(c) Preparations from the chloroform precipitate may be made surprisingly thick without impairing visibility and with corresponding increase in concentration. Such preparations adhere to the slide in a superior manner and dry rapidly and smoothly.

(d) When light hydrocarbons are used, bacilli may also be found in considerable numbers in the bottom of the tube, necessarily decreasing concentration in the surface layer.

COMPARISON WITH OTHER METHODS

A small series of counts for comparison with other methods have been made.

We have used the methods of Petroff (7), Greenfield and Anderson (8), Ellermann and Erlandsen (9), Calmette (10), autodigestion (11), etc., which involve the use of various alkalis and sedimentation. These methods have in our hands given concentrations of three to four over direct smears made from shaken specimens. Distribution was invariably poor, and the morphology and staining properties of the bacilli usually impaired. With antiformin we have frequently seen complete dissolution of the bacilli.

Comparison with the various hydrocarbons has shown gasoline and ligroin to give excellent preparations with, we think, preference to the latter. Concentration has been ten to twenty times higher with these agents. Acetone, ether, etc., have been of relatively little value.

With chloroform we have obtained routine concentration of 90 to 240 over the direct smear and have thought that both staining properties and distribution were superior to those obtained with the other reagents. In our earlier work we demonstrated bacilli a number of times by the use of chloroform when we were unable to find them with gasoline.

RESULTS OF CONTROL GUINEA-PIG INOCULATIONS

Forty-seven successful guinea-pig inoculations were obtained out of an attempted 50. Specimens inoculated had for the most part been always negative by the direct-smear method, the few exceptions having not been positive for several months. Specimens were shaken in mechanical shaker, to ensure rough distribution of bacilli, and 1 cc. of the otherwise untreated material injected into the inguinal region. The remainder of the specimen was examined by the chloroform-concentration method as described. In animals, called positive at autopsy, abundant acid-fast bacilli were invariably demonstrated by direct smear in pus from the regional glands. Autopsies on negative cases were conducted by a disinterested pathologist[2] and sections of organs made in all doubtful cases.

The correlation has been as follows:

Twenty-four specimens negative by concentration gave also negative guinea pigs, an agreement of 100 per cent.

[2] Kindness of Dr. F. H. Luney, Institute of Public Health, London, Ontario.

Twenty-three specimens positive by concentration gave 19 positive guinea pigs, an agreement of 83 per cent. Thus, we have 4 animals negative for tuberculosis after inoculation with specimens found positive by concentration.

A study of these four cases in an effort to find a clue to the disagreement revealed the following facts: 1. Bacilli were scanty, even by concentration in all four cases. 2. Three of the four cases had been positive by direct smear, one four months, one seven months, and one sixteen months previously. The fourth had had ten consecutive negative direct-smear examinations at the same time as the positive concentration. 3. All four showed typical moderately to far advanced parenchymatous tuberculous lesions and were clinically ill. The possibilities to consider are (1) that the bacilli seen were incorrectly called tubercle bacilli, (2) that the bacilli entered the specimens through technical error after the material for animal inoculation had been separated and (3) that the bacilli were too few in number or too low in virulence to infect the guinea pigs.

We are, although open to the criticism of prejudice, inclined to the latter view. As previously mentioned, the most detailed precautions were observed to eliminate contamination. None apparently occurred with the negative specimens. The presence of outstanding parenchymatous tuberculosis in all four cases showing disagreement, the demonstration of tubercle bacilli by the direct method some months previously in three out of four of the cases showing disagreement, together with the fact that only one out of 34 that had shown bacilli by the direct method on any previous occasion was negative by concentration, leads us to believe that it is unlikely that tubercle bacilli were not really present in at least the three previously positive cases. The amount of material inoculated was smaller than ideal while, as before mentioned, the bacilli in each case were scanty even by concentration. Larger amounts of material have the very decided disadvantage of causing high immediate mortality among the animals due to acute nonspecific infections. It is possible that some of the concentration-negative group would have shown positive guinea pigs had larger amounts been inoculated.

It is interesting that Wankel (12) recently reports finding two-thirds of tuberculous subjects with sputum negative to guinea pig inoculation, but an increase of one-third positives over other methods (presumably direct examination).

Taking the above data therefore as a whole, it seems most probable that at least the three cases, previously positive by direct smear, did

actually contain tubercle bacilli as demonstrated by concentration, and that the guinea pig is of limited sensitiveness to tuberculous infection, perhaps due to paucity of bacilli or perhaps to low virulence of bacilli. Granting however a maximum error of 17 per cent too many positives, the method is still invaluable as showing a high increase of positive findings over the repeated direct method. As in the latter, it is, of course, true that a single positive examination should not be accepted for diagnosis in view of the possibilities of contamination and technical and clerical errors.

SUMMARY

1. An improved technique for the demonstration of tubercle bacilli in morbid products is described.

2. Among the clinically tuberculous the tubercle bacillus has been demonstrated in 57 per cent of cases negative by the direct method on repeated examinations.

3. Bacilli have been demonstrated in the sputum of persons considered nontuberculous, necessitating a change in diagnosis.

4. The results obtained well justify the increased expense and labor involved.

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THE INFLUENCE OF LIGHT ENERGY (SUNLIGHT) ON THE HYDROGEN ION CONCENTRATION OF THE BLOOD[1]

FRANK C. BALDERREY AND OTAKAR BARKUS

The actual reaction of the blood varies within very narrow limits, even in the presence of marked pathological conditions. It possesses a hydrogen ion concentration less than that of a neutral liquid and is slightly alkaline. In health it has been found to average pH 7.45. The arterial blood is slightly more alkaline than the venous blood, due to the greater amount of CO_2 in the latter. The constancy of the reaction is maintained by two factors: first, the so called buffer substances of the blood, namely, the alkaline carbonates, the alkaline phosphates and the alkaline salts of the proteins, and, secondly, the regulatory action of the lungs and kidneys.

Diseases that produce a diminution in the amount of alkali in the blood available for the protection of the reaction or, as it is usually expressed, a diminution in the alkaline reserve, are diabetes, in which there is imperfect oxidation of fats, giving rise to the production of acids, particularly beta-oxybutyric acid, infectious diseases in which destruction of tissue is extensive, destruction of the liver, metabolic disturbances of pregnancy, starvation, acid poisoning, chronic nephritis, and cardiac disease accompanied by decompensation and dyspnea. Alkalosis, as a condition, may be present in pyloric obstruction, produced by vomiting and continued loss of hydrochloric acid with the gastric juice. Slight changes in the reaction of the blood, tending to an increase in the alkalinity, have been observed following radiations with X-rays and heat.

As a further study of the action of light energy, the following changes in the pH of the blood are reported. All of the determinations were made upon patients with some manifestation of tuberculosis. The reaction of the blood was determined in 63 patients. Of this number 47 were being treated with heliotherapy and 16 with the usual "rest cure."

[1] From the Department of Research of the J. N. Adam Memorial Hospital, under the direction of John H. Pryor (*deceased*), Consultant-in-chief, and Horace LoGrasso, Superintendent.

The object of the work was to determine the effect of light energy (sunlight) upon the reaction of the blood; in conjunction with this the influence of pigmentation, or the degree of pigmentation, and variations in the intensity of sunlight were determined by presence or absence of clouds, temperature and humidity upon the reaction.

The action of light energy was to be judged from the results observed first, in cases subjected to solar radiations of from 45 to 90 minutes, and second, those not exposed to direct light but resting in a reclining position for the same period. All observations were made between the hours of 9:00 and 10:30 A.M., from June 11 to July 12, 1923. The methods employed were as follows:

(1) All specimens of bloods to be taken during a period of fasting, the last full meal permitted to be at 5:30 P.M. on the day previous to the determinations. (2) Specimens of blood for examination to be drawn before and after the radiation and rest periods. (3) Blood to be taken from the veins of the forearm and collected under oil (liquid albolene). (4) Determinations to be made by the Cullen colorometric method. (5) The degree of pigmentation to be determined by means of Robertson pigmentometers.

The effects of different modes of treatment or, more strictly speaking, the influence of light energy upon the reaction of the blood, must be considered from two viewpoints: first, as to the immediate effect of radiation with sunlight or the observance of a rest period and, second, as to the effect of repeated daily radiations or rest periods upon the pH of the blood. Taking then the determinations before either radiation or rest, as the individual's normal reaction of the blood, we find a marked difference in these two groups. Those undergoing rest cure showed a pH of 7.39, or practically a normal reaction, but those who were receiving heliotherapy showed a pH of 7.54, a slight increase over that which is considered normal in health. This apparently establishes the fact that light energy has a definite and specific action upon the reaction of the blood. As additional proof of this, the following figures only go to substantiate the foregoing statement and in addition show the immediate effects of light energy upon the reaction of the blood. It must also be borne in mind that a slight alkalosis has been shown to exist in those patients receiving solar radiations, and any further increase in alkalinity perhaps is less likely to occur during a single radiation.

The immediate effects may be summarized as follows:

TREATMENT	INCREASE	NO CHANGE	DECREASE	AVERAGE pH BEFORE	AVERAGE pH AFTER	AVERAGE INCREASE
Heliotherapy	23 or 49%	19 or 40%	5 or 11%	7.54	7.59	0.05
Rest cure	6 or 37%	6 or 37%	4 or 25%	7.39	7.39	

The relationship of the degree of pigmentation to the reaction of the blood may be studied from the following table. Number 8 represents a chocolate brown color and numbers 7 and 6 correspondingly lighter shades of brown.

DEGREE OF PIGMENT	INCREASE	NO CHANGE	DECREASE	AVERAGE pH BEFORE	AVERAGE pH AFTER	AVERAGE INCREASE
No. 8	8 or 57%	6 or 43%		7.6	7.62	0.02
No. 7	9 or 53%	6 or 35%	2 or 11%	7.46	7.56	0.10
No. 6 or less	6 or 40%	6 or 40%	3 or 20%	7.55	7.6	0.05
Total of pigment	23 or 50%	18 or 39%	5 or 11%	7.54	7.59	0.05
None (rest cure)	6 or 37%	6 or 37%	4 or 25%	7.39	7.39	

Note: (One case, negro, not included in above group.)

The influence of weather conditions upon the reaction of the blood in these cases resulted as follows: In the description of the character of the day as either bright or cloudy, it must be added that the work was done only on days on which the sun shone, and the days designated as cloudy were those on which fleeting clouds obscured the sun for short intervals throughout the time of radiation. The days described as bright had a maximum temperature of 82 and a minimum of 71 and the humidity was 76; and those that were cloudy a maximum temperature of 76 and a minimum of 56 and the humidity was 78.

CHARACTER OF DAY	INCREASE	NO CHANGE	DECREASE	AVERAGE pH BEFORE	AVERAGE pH AFTER	AVERAGE INCREASE
Bright	13 or 54%	9 or 37%	2 or 8%	7.43	7.60	0.17
Cloudy	10 or 43%	10 or 43%	3 or 17%	7.51	7.53	0.02

DISCUSSION

Considering, then, these results from the standpoint of the action of light energy (sunlight) upon the human body, it may be said that radiations with this source of energy change the reaction of the blood, increasing its alkalinity. The exact manner in which this is accomplished

cannot be definitely stated at present, but it is reasonable to suppose that it is brought about by a diminished concentration of the carbon dioxide in the blood and alveolar air. This phase is at present under investigation. Those wave-lengths of the solar spectrum, most active in or solely producing this change, are also being studied and will be reported later. However, from the observations that heat will increase the alkalinity of the blood, the supposition may be made that the wave-lengths most active in producing it are those of the visible spectrum with greater wave-length, and those of the invisible spectrum, the infrareds. Sonne has shown that by means of the luminous rays the temperature in the tissue may be raised to a higher degree than by the use of the infrareds. In our own experience we have found that insolation is more quickly produced, and the severity of the insolation most marked, when caused by wave-lengths between 480 and 700. Loewey and Richter, by keeping animals in a thermostat room at a high temperature, were able to develop in these animals a greater defense against infections than in those kept at room temperature. Murphy and Sturm have demonstrated that the average length of life after inoculation is greatest in heated animals. Our own experience is similar, as we have observed that guinea pigs infected with tuberculosis and subjected to the energy of different portions of the spectrum, live longer, make greater gains in weight and maintain normal weight best under red, wave-lengths 680 to 700, and green, wave-lengths 480 and 700.

Associated with these findings, and an established fact as to the action of light, is the increase in lymphocytes reported by Hyde and LoGrasso, our own investigations in this line merely adding to the substantiation of their earlier work.

CONCLUSIONS

1. Exposure of the human body to radiations with light energy (sunlight) increases the alkalinity of the blood.

2. The degree of pigmentation present has a direct influence on the change in the reaction of blood. The greater the amount of pigmentation the more marked the change in the pH of the blood. May it not be true that this increased pigmentation acts as a protective measure against the extremely short wave-lengths, thus enabling the body to withstand longer periods of radiation, increases penetration and favors the conversion of light energy?

3. Considering that the determinations as to the hydrogen ion concentration of the blood, before and after radiation, were made with light rich in the longer wave-lengths and when the extremely short wave-lengths were at a minimum, in all probability the wave-lengths most active in this reaction of the body to radiation are those of the visible spectrum. Variations in the intensity of light, as evidenced by continuous bright sunlight, increased temperature and lessened humidity, materially influence the effect of light upon the reaction of the blood.

The participation of Mr. Otakar Barkus in this study was made possible through the efforts of the late Dr. John H. Pryor and the funds donated by Mrs. Joseph T. Jones of Buffalo, New York.

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BESREDKA'S TUBERCULOSIS ANTIGEN AND THE COMPLEMENT-FIXATION REACTION

REPORT ON 1199 TUBERCULOUS AND NONTUBERCULOUS PATIENTS[1]

B. M. FRIED

The complement-fixation test in tuberculosis is based on the same theoretical principles (Bordet-Gengou phenomenon) as the Bordet-Wassermann test in syphilis.

As in the Bordet-Wassermann in syphilis, the purpose of the complement-fixation reaction in tuberculosis, from a practical point of view, is to furnish a diagnosis in early, doubtful and unsuspected cases, and to control the treatment. Technically, the test differs from the Bordet-Wassermann only in the use of a different antigen. While in syphilis, as is well known, the antigen consists of an alcoholic extract of a liver from an heredosyphilitic or normal human being or animal (guinea pig, ox) heart, in tuberculosis results are obtained only with the use of an antigen consisting of tubercle bacilli or their extracts.

Since Widal (1), who was first to apply the Bordet-Gengou phenomenon to tuberculosis, using an emulsion of living tubercle bacilli as antigen, the test has been tried by numerous workers, with, however, conflicting results.

With Besredka (2) the test entered an experimental phase. This author first tried the test, using his own antigen on laboratory animals (rabbits and guinea pigs) by inoculating them with human or bovine types of tubercle bacilli. According to his experiments, specific antibodies, detectable by the complement-fixation test, appear very early in experimental animals; on the fourth day after inoculation in guinea pigs and on the fifteenth to eighteenth day in rabbits.

Besredka affirmed that, by killing the animals at the time when the test first became positive, he could not discover in their viscera any macroscopic tuberculous lesions.

A good deal of work has been performed in the last few years on the complement-fixation test in tuberculosis with the use of Besredka's antigen (so called egg-antigen).

[1] From the Boston Sanatorium and the Peter Bent Brigham Hospital, Boston.

Hruska and Pfenninger (3) and Brocq-Rousseu and Urbain (4) applied the test for the detection of specific antibodies in tuberculous cattle. The blood to be tested was taken from freshly killed animals. Therefore, the authors were able to verify the results of the test, and in this respect, as was pointed out elsewhere, their work had the value of an experimental study.

In 304 tuberculous sera examined, the test was positive in from 84 to 95 per cent, according to the stage of the process. In 92 normal sera the test agreed with the findings in the abattoir in 97.8 per cent of the cases. Hruska and Pfenninger conclude that "the fixation test with the egg-antigen is called to render important services in the fight against bovine tuberculosis."

In bone and joint tuberculosis the test, with the use of Besredka's antigen, was applied for the first time by Mozer and Fried (5) (Hôpital Maritime de Berck-plage, France) on 1005 patients.

It is rather of interest to note that the serum of patients with external tuberculosis was considered, up to the time of Mozer and Fried's work, to be deprived of specific antibodies. Calmette (6) says, "If patients with surgical tuberculosis show no signs of lymphatic or pulmonary tuberculosis, they react very violently to tuberculin, yet generally their blood contains no antibodies."

The cases of tuberculosis studied by Fried and Mozer with the use of Besredka's antigen included lesions of the bones exclusively, without any clinically detectable visceral or lymphatic involvement. The failure of Calmette to detect specific antibodies in such lesions is certainly due to the antigen used by him.

The importance of a biological test in the diagnosis of a surgical tuberculous lesion is certainly not less than in the case of a visceral lesion. The difficulties in the differential diagnosis between syphilitic, tuberculous and other kinds of bone or joint lesions, not only in the early stages of the disease, but also in the advanced stages, are rather widely known. Again, the clinician is not infrequently embarrassed in the determination as to whether the bone or joint lesion is active, progressive or arrested, quiescent, etc.

In the classification of our clinical material as regards activity, we were guided by a somewhat arbitrary division.

We estimated that a tuberculous spine (Pott's disease) or hip (tuberculous coxitis), in an overwhelming majority of cases, is active (that is, progressive) for about three years; and a cold abscess of the knee or other

osteoarticular processes for about two years from the onset of the disease. After this time, the lesion in the large majority of cases is arrested or quiescent. It is understood that the gravity of the lesion is always to be taken into consideration.

Thus, our material (1005 cases) has been classified according to the *duration* of the lesion and its *gravity*.

Table 1 shows the results obtained.

In 44 cases of cervical tuberculosis lesions up to two years' duration gave 48 per cent of positive results, while those of more than two years' duration, most of them of 4, 5 and 6 years, and presumably arrested or quiescent, gave only 13.3 per cent.

As can be seen from the table, lesions up to three years in Pott's disease and tuberculous coxitis and up to two years in cold abscess of the knee and small osteoarticular lesions, in the great majority supposedly active, furnished positive results in from 70 to 77 per cent of cases. Beyond

TABLE 1

DURATION OF LESION	POTT'S DISEASE: PER CENT OF POSITIVE RESULTS	TUBERCULOUS HIP: PER CENT OF POSITIVE RESULTS	COLD ABSCESS OF KNEE: PER CENT OF POSITIVE RESULTS	SMALL TUBERCULOUS OSTEOARTICULAR LESION: PER CENT OF POSITIVE RESULTS
From 0 to 3 years.....	77	75	76.2	70
Above 3 years.....	26.94	28.5	36.6	34.28
With sinuses and poor prognosis...	26.6	24.4	14.28	

this period, when the lesion is supposed to be in a large majority arrested or quiescent, the positive results vary from 26 to 34 per cent. Lesions with long-standing sinuses and poor prognoses furnished from 14.28 to 26 per cent of positive results. (We shall comment on the latter figure in the discussion of the prognosis.)

As a result, Mozer and Fried concluded:

1. The complement-fixation test in surgical tuberculosis with the use of Besredka's antigen has the same value as the Bordet-Wassermann in osteoarticular syphilis. Being inferior to the clinical picture as an index of the degree of activity of a lesion, the test is, however, particularly important in cases in which the lesion is deep. A positive test always indicates the appearance either of a cold abscess or a relapse.

In a later review on the complement-fixation test in pulmonary and surgical tuberculosis, performed with the use of Besredka's antigen by

different workers up to 1921, Fried and Mozer (7) reached the following conclusions:

1. The test (in surgical and pulmonary tuberculosis) with the use of Besredka's antigen is a reliable method in the diagnosis of the disease at its onset.

2. A positive reaction indicates, except in rare cases, the presence of an active tuberculous lesion. On the other hand, a negative test does not exclude the diagnosis of tuberculosis.

3. The test with the use of Besredka's antigen deserves a place in the first rank of the laboratory methods in the diagnosis of tuberculosis.

In visceral tuberculosis the test with the egg-antigen has been used with very favorable results by Bronfenbrenner (8), Inman (9), Debain and Jupille (10), Kuss and Rubinstein (11), Ichok (12), Massias (13), Grumbach (14), Lydia Rabinowitch (15), Pellier (16), Bass (17), Fried (18), Sévi (19), Aviragnet, (the two latter in children), and many others.

Lanzenberg and Jaquot (20), who apply the test with Besredka's antigen as a routine in the antituberculosis dispensary *de l'Office d'Hygiene* in Paris, consider the reaction a great help in the immediate elimination of the suspicious and nontuberculous cases.

TECHNIQUE

Hemolytic System: An antisheep, hemolytic system is used in this study: 1 cc. of a dilution of 1 to 5000 is the unit in our system.

Complement: Complement is obtained from a guinea pig, killed just before the test is performed. The serum (complement) is separated from the clotted blood by means of a centrifuge.

Red Cells: An emulsion, 1 to 30 in saline solution, of thoroughly washed sheep's red cells is used.

Human Serum: Blood is collected under aseptic precautions, and the serum is separated after being kept with the clot in the ice-chest for about 24 hours. The serum is inactivated for ½ hour at 56°C.

Antigen: As an antigen we used Besredka's *Bacillary Emulsion.* This is a 4 to 6-day-old culture of a human strain of tubercle bacilli grown on a liquid egg medium (Besredka's medium (22)) and killed by heat. The medium consists of the yolk of egg, distilled water and sodium hydroxide. There is no glycerine or broth in the medium. Besredka obtains a profuse growth of tubercle bacilli on his medium in 48 to 72 hours. This is the 4 to 6-day-old culture, which, according to Besredka, furnished the best antigen. The antigen is titrated in the usual way and one-sixth of the anticomplementary unit is used in the test.

The test: The freshly obtained complement is used in a dilution of 1 to 15 (1 of complement and 14 cc. of saline) and is always titrated before the test is performed.

Two tubes are used in the test. Each of them contains serum 0.2 cc. and antigen 0.3. *This is well mixed and kept for 15 minutes at room temperature.* Titrated complement is then added: to the first tube the amount corresponding to tube 5 of table 2 (next after the M.H.D.); to the second tube the amount corresponding to tube 6 of the table. Controls are placed for the anticomplementary properties of each serum. *This is incubated for 75 minutes in a water bath of 38°C.* One-half cubic centimetre of an emulsion of red cells (1 to 30) and four units of amboceptor are then added to each tube and this is incubated in a bath for 30 minutes at 38°C. The total volume of 2 cc. is

TABLE 2

Titration of the complement

	TUBE 1	TUBE 2	TUBE 3	TUBE 4	TUBE 5	TUBE 6
Complement, 1:15	0.05	0.10	0.15	0.20	0.25	0.30
Red cells, 1:30	0.50	0.50	0.50	0.50	0.50	0.50
Amboceptor	4 units	4 units	4 units	4 units	4 units	4 units
Saline, q.s. to make up a total volume of 2 cc.						
	30°–38°C.					
	N. H.	N. H.	P. H.	C. H.	C. H.	C. H.

always made up by adding saline before the first incubation. The red cells are always sensitized 15 minutes before use. The results of the test are read immediately following the second incubation.

CLINICAL MATERIAL

The clinical material reported consists of

1. Nontuberculous patients under treatment at the Peter Bent Brigham Hospital.
2. Nontuberculous patients from the Out-Patient Department of the same hospital.
3. Tuberculous patients under treatment at the Boston Sanatorium.

1. NONTUBERCULOUS PATIENTS: HOUSE CASES

Having been largely employed in positive cases of tuberculosis, the test with Besredka's antigen has not as yet been the object of an extensive study on nontuberculous clinical material.

It is rather clear that a biological test to be of any clinical value must be, first of all, specific. To determine the specificity of Besredka's antigen Urbain and Fried (22) proceeded as follows: (a) They prepared antigens from various bacteria (streptococci, staphylococci, pneumococci, B. coli, Eberth's bacillus, paratyphoid, etc.) and performed the complement-fixation test by using these antigens in the presence of an immune tuberculous horse serum and human tuberculous sera. (b) Employing Besredka's tuberculosis antigen, they performed the fixation test in the presence of various nontuberculous sera (antidysenteric, antiplague, antimeningococcic, antidiphtheritic, etc.).

As a result of their experiments, the authors concluded:

1. An immune tuberculous horse serum fixed large quantities of complement (five thousand units) in the presence of Besredka's antigen.

This same serum in the presence of other antigens (streptococcic, staphylococcic, pneumococcic, B. coli, paratyphoid, glanders bacillus, anthrax, and B. subtilis) acts as a normal serum; that is, it does not fix the complement.

2. The sera of tuberculous patients which fix several units of complement in the presence of Besredka's antigen are indifferent in the presence of the nonspecific antigens previously enumerated.

In only three cases (out of 20 sera) was a positive fixation noted in the presence of an antigen prepared from Klebs-Loeffler's bacillus, and in 2 cases (out of 15 sera) in the presence of an antigen prepared from *B. subtilis*.

3. The sera of horses immunized against various other bacteria and toxins failed to show any appreciable fixation in the presence of Besredka's antigen, acting, in general, like normal horse serum. Only antidiphtheritic horse serum showed a notable fixation property, very much inferior, however, to the sera of horses prepared with tubercle bacilli.

4. The sera of patients suffering from disease other than tuberculosis (typhoid fever, erysipelas, etc.) did not fix complement in the presence of Besredka's antigen. Only the sera of diphtheria patients seemed at first glance to be the exception to the rule. In reality, it occurred practically always in patients who had received antidiphtheritic serum previous to the blood examination.

The fixation of complement in the presence of a horse serum immunized against diphtheria, as well as of serum of patients treated with antidiphtheritic serum in the presence of a tuberculosis antigen, is

interesting in that the chemical composition of the Klebs-Loeffler bacillus, as is known, closely approaches that of Koch's bacillus.

Rieux and Bass, using Besredka's antigen, always secured a negative result in measles, scarlet fever and whooping cough.

As has been stated the actual study on nontuberculous sera was done on patients from the medical and surgical wards of the Peter Bent Brigham Hospital and from the Out-Patient Department of the same hospital. According to the disease, this material may be arbitrarily classified as follows:

Heart diseases (chronic myocarditis, valvular disease, subacute bacterial endocarditis, disease of the pericardium, auricular fibrillation, hypertension, angina pectoris, aortitis and aneurysm of aorta)	105
Lung diseases (lobar and lobular pneumonia, bronchitis, emphysema, asthma, asthmatic bronchitis, lung abscess)	55
Gastrointestinal diseases (gastritis, gastric ulcer, hyperchlorhydria, appendicitis, ulcerative colitis, etc.)	47
Liver and gall bladder (hepatitis, cirrhosis of liver, jaundice, cholecystitis and cholelithiasis)	18
Kidney diseases (nephritis, hydronephrosis, renal calculi, pyonephrosis, pyelonephritis, uremia)	46
Diseases of the pelvic organs (cystitis, chronic salpingitis, prostatitis, endometritis, dysmenorrhoea, hypertrophy of prostate, etc.)	40
Blood diseases (pernicious and secondary anemia)	20
Rheumatism and arthritis	20
Arteriosclerosis	8
Tonsillitis and pharyngitis	12
Diabetes, gout, hyperthyroidism	44
Syphilis	51
Tumors:	
Carcinoma	17
Sarcoma of lungs and pleura	2
Endothelioma	9
Tumor of brain and spinal cord	32
Nervous diseases (neurosis, paralysis agitans, psychoneurosis, paresis, hysteria, epilepsy, etc.)	63
Miscellaneous (pellagra, typhoid fever, polycythemia vera, trichiniasis, actinomycosis, chorea, alcoholism, poisoning, debility, pregnancy, fracture of bone, carbuncle, hernia, no disease)	50
Total	639

Of 639 patients studied, 30 or 4.7 per cent were clinically diagnosed as tuberculosis and 609 as nontuberculous. The complement-fixation test with Besredka's antigen was positive in 24 out of the 30 cases.

The following are abstracts from the histories of each of the six cases clinically diagnosed as tuberculosis, but with negative-complement fixation tests:

Clinically, tuberculosis. Complement-fixation test negative

Case 1: Med. no. 21,360: S. C.: Past history suggests tuberculosis. Physical examination shows slight dulness and prolongation of breath sounds at right apex. No tubercle bacilli found in the sputum on repeated examination. Discharged improved.

Case 2: Med. no. 20,998: V. J.: Sixty-seven years old. Ill for six weeks. Clinical diagnosis, pulmonary tuberculosis and pleurisy with effusion. Inoculation of pleural fluid into guinea pig negative for tuberculosis. Sputum negative on repeated examinations for tubercle bacilli.

Case 3: Med. no. 20,361: C.: Tuberculous bronchopneumonia. Marked emaciation, rapid loss of weight. Poor prognosis. Transferred to sanatorium unimproved.

Case 4: Med. no. 21,246: W.: Very emaciated. No sputum. X-ray findings suggest advanced tuberculous bronchopneumonia, that approaches in distribution a diffuse metastatic carcinoma. Discharged unimproved.

Case 5: Sur. no. 18,496: E. L.: Tuberculosis of fourth ventricle, verified by autopsy. The patient died 19 days after the test was performed.

Case 6: Med. no. 21,608: W. Y.: A markedly emaciated man. Rapidly progressing tuberculous bronchopneumonia. Tuberculous laryngitis. Poor prognosis. Patient died 17 days after test was performed.

As can be seen from the six above reported patients who failed to react to the test, two (nos. 5 and 6) died within twenty days after the blood was examined. In two instances (nos. 3 and 4) it concerned emaciated persons with a very poor prognosis. In cases 1 and 2 the clinical diagnosis of tuberculosis could not be verified. Cases 3, 4, 5 and 6 are interesting in relation to the observation of Besredka (2) and Besredka and Netter, namely, that the test is very often negative in advanced tuberculosis with a poor prognosis as well as in rapidly failing cases (tuberculous meningitis).

In our study on bone and joint tuberculosis (*loc. cit*) we observed that, while in the initial, evolutionary stage of the disease, the percentage of positive tests was high, in the stage of healing as well as dying patients (long standing suppuration with amyloid degeneration of viscera) the percentage of positive tests with Besredka's antigen was very low (see table 1).

In two instances the physical examination disclosed no tuberculosis, while the test was positive. The test, however, was confirmed at autopsy in one instance and by surgical intervention in the second.

The following are abstracts from the histories of the two cases:

Case 7: Med. no. 20,826: L. E.: Forty-five years of age. *Lungs:* tactile fremitus normal, no impairment to percussion. Breath sounds, spoken and whispered voice transmitted normally. No râles. X-ray negative.

At autopsy, the parenchyma of the lungs showed no tuberculosis. A markedly enlarged lymph node was found, which on microscopic examination showed "the normal structure of the node to be destroyed by a rather extensive tuberculosis. There are several large, caseous areas composed of a structureless, pink-staining material and surrounded by fibrous tissue infiltrated with small round cells. In addition there are many single and conglomerate tubercles scattered throughout the section." (S. B. Wolbach.)

Case 8: Sur. no. 19,263: S. J.: Twenty-three years old. *Clinical diagnosis:* Lymphosarcoma or Hodgkin's disease. Tuberculosis complement-fixation test positive. Ill for six weeks. Strong and well developed. Physical examination shows cervical glands markedly swollen in the anterior and posterior triangles, particularly on the left side. They are firm and discrete. X-ray of chest normal. No evidence of glandular involvement.

The patient was transferred to the surgical ward for operation. *Pathological report:* Section shows a tuberculous lymph node with only a small portion of lymphoid tissue remaining. The centre of the node is caseous and is surrounded by typical tubercles. Tubercle bacilli are found in a smear. *Pathological diagnosis:* Tuberculous lymphadenitis. (S. B. Wolbach.)

In eleven instances out of 609, or in 1.8 per cent of all cases examined, the test was found to be positive, while on clinical examination no tuberculosis could be found. These cases did not come to autopsy or surgical intervention.

2. NONTUBERCULOUS PATIENTS: OUTDOOR CASES

Because of the results obtained on thoroughly studied nontuberculous hospital cases, we considered it of interest to study the test on patients from the Outdoor Department of the Peter Bent Brigham Hospital. The complement-fixation test with Besredka's antigen was done on 160 such patients. Not one of the 160 patients had been diagnosed as tuberculous in the Outdoor Department, while the complement-fixation test was positive in six instances, or 3.75 per cent, and negative in 154.

The diagnosis of the 6 patients was as follows: convulsions (cause unknown), dermatitis venenata, deferred, no diagnosis, coccydynia, chronic gastric indigestion.

3. TUBERCULOSIS PATIENTS

The tuberculous material studied was taken from the Boston Sanatorium. The diagnosis of tuberculosis was based on clinical observation, X-ray examination and positive sputum. The study was done in con-

junction with the above reported normal sera, thus serving as a control. The sera of 400 patients were examined and all patients had active tuberculosis of various degrees of activity. According to the classification of the American Sanatorium Association the patients may be divided into Incipient 56, Moderately Advanced 115 and Far Advanced 229, or a total of 400.

The differences in percentages of positive results between Incipient, Far and Moderately Advanced cases vary only from 1 to 2 per cent. Of the total number of 400 tuberculous patients, 359, or 89.75 per cent, showed a positive result with Besredka's antigen.

SYPHILITIC SERA AND THE TUBERCULOSIS ANTIGEN

Special attention has been attracted by the fact that syphilitic sera give complement-fixation tests in the presence of a tuberculosis antigen. This was attributed by some writers to the presence of lipoids in the tuberculosis antigen, which, as is known, make up the essential part of the usual syphilitic antigen. The figures of the nonspecific fixation are estimated by the first writers on the subject as varying between 20 and 30 per cent.

Of the sera examined, 51 were of syphilitics of all stages (roseola, syphilitic gumma and tabes) with strongly positive Wassermanns, but without any evidences of tuberculosis. In 6 instances, or 11.76 per cent, the complement-fixation test with Besredka's antigen was positive.

However small the figures of the nonspecific fixation are, we, as a rule, perform the test routinely with a tuberculosis and a syphilitic antigen, and in the presence of a positive Wassermann a positive fixation for tuberculosis must be accepted with caution.

THE STABILITY OF BESREDKA'S ANTIGEN

There is a prevalent opinion among serologists that the bacillary-emulsion antigen gives the best results in the complement-fixation test in tuberculosis. It was, however, reported by some workers that such an antigen loses its antigenic power very quickly and, in addition, becomes to a large degree anticomplementary.

In order to test the stability of Besredka's bacillary-emulsion antigen we proceeded as follows: The antigen, titrated in the presence of an immune tuberculous horse serum for its antigenic power, was divided into four tubes, two of which contained the mother solution, and two

others were in the diluted state, as for the test. One tube, with the mother solution, and another with the diluted antigen, were kept in the ice chest at 6°C., while two other tubes with similar contents were placed at room temperature in a dark place. This was titrated from time to time.

After twelve months the mother solution, as well as the diluted (those kept in the ice-chest as well as those kept at the room temperature), did not lose any of its antigenic power and did not increase its anti-complementary properties.

The titre of the antigen was as follows: 1/10 of a dilution of one to ten thousand of the immune serum fixed eight units of complement in the presence of 0.3 cc. (1/6 of the anticomplementary unit) of Besredka's antigen.

We conclude, therefore, that Besredka's antigen can be preserved indefinitely.

DISCUSSION

The value of the complement-fixation test in tuberculosis is contested principally for two reasons: (1) the occurrence of negative results in undoubtedly active tuberculosis, and (2) the occurrence of falsely positive tests.

"Falsely negative reactions," says Kolmer (23), in a review on the complement-fixation reaction in syphilis, "will probably always occur for biological reasons, because, no matter how sensitive a test may be made, it cannot detect in the serum or spinal fluid something that is practically absent, and it would appear that in some cases of latent syphilis the activity of spirochetes is so reduced that demonstrable amounts of *reagin* are not produced."

As regards tuberculosis, whether the fault in the production of antibodies lies in the reduced activity of the invader alone or whether the host himself must also be taken into consideration, is as yet to be investigated.

Calmette (*loc. cit., p. 505*) believes that falsely negative results in the complement-fixation test in tuberculosis are often due to the *excess* of specific antibodies in the serum. The same author found also that some tuberculous sera possess the peculiar property that he calls *inhibitrice*, which interferes with the fixation of the complement. Such sera, if added to a mixture of antigen and antibody, before the complement is added, interfere with the fixation of the latter.

Some workers (Bezançon and Serbonnes, and the writer himself) have observed that a previously negative test often gives a positive fixation a few days later on a new sample of blood. The importance of a repeated blood examination in doubtful cases cannot therefore be overemphasized.

Falsely positive results (with the use of Besredka's antigen) are due, we believe, to

1. Errors in technique. The test, exactly as in syphilis, requires skill and experience, and even when done carefully mistakes are sometimes unavoidable as in any biological test.

2. Errors in clinical diagnosis of tuberculosis. Not infrequently the clinician fails to make a diagnosis of tuberculosis and, as a result, the serological test is contested.

3. The discrepancy existing between the pathological and clinical conception of activity. Case 6, above reported, illustrates a condition of tuberculosis active pathologically but with no signs of tuberculosis clinically.

The French clinicians Rist and Ameuille, discussing the complement-fixation reaction with the use of Besredka's antigen, said, "The complement-fixation test, studied systematically and without *parti pris*, cannot but enable us to glean greater information on the problems of tuberculosis."

It may be added, "and the further study of the pathology of tuberculosis cannot but enable us to glean greater information on the sero-reaction in tuberculosis."

SUMMARY

The complement-fixation test with the use of Besredka's tuberculosis antigen was performed on 1199 tuberculous and nontuberculous patients.

Six hundred and thirty-nine of these patients (nontuberculous) were under treatment at the Peter Bent Brigham Hospital and were ill with diseases of the heart, lungs, liver, kidney, etc. Thirty, or 4.8 per cent of the 639 were clinically diagnosed as tuberculosis. The complement-fixation test with Besredka's antigen was positive in 24 instances out of the 30.

Of the six patients who failed to react to the test, two died within 20 days, following the blood examination; in two, the involvement of the lungs was very extensive, the patients emaciated and the prognosis extremely poor. In two other cases, the clinical diagnosis of tuberculosis

could not be definitely confirmed, either by X-ray examination or by positive sputum. An abstract of the history of the six cases has been given. Of the 609 patients diagnosed as nontuberculous the test agreed with the clinical findings in 598 instances, or in 98.2 per cent. In only eleven instances of these 609, or in 1.8 per cent, was the test positive, while clinically no tuberculosis could be discovered.

One hundred and sixty patients, also nontuberculous, were from the Outdoor Department of the same hospital. In 154 instances, out of 160, the test agreed with the clinical diagnosis, while in six instances or in 3.75 per cent, the test for tuberculosis was positive. The clinical diagnoses of the 6 cases were as follows: convulsions (cause unknown), deferred, no diagnosis, coccydynia, chronic gastric indigestion, dermatitis venenata.

Four hundred sera were taken from tuberculosis patients under treatment at the Boston Sanatorium. Fifty-six of these were incipient, one hundred and fifteen moderately advanced and two hundred and twenty-nine far advanced.

Three hundred and fifty-nine, or 89.75 per cent, of the 400 showed a positive complement-fixation test with Besredka's antigen.

Fifty-one sera from syphilitic patients, with a strongly positive Wassermann without clinical signs of tuberculosis, were examined. Only 6, or 11.76 per cent, of them fixed complement in the presence of the tuberculous antigen.

The stability of Besredka's tuberculous bacillary-emulsion antigen was studied from the point of view of its antigenic power, as well as its anticomplementary properties. After twelve months it was found that the antigen still retained all of its original properties.

The technique used was given in detail above.

CONCLUSIONS

1. The complement-fixation test in tuberculosis, with the use of Besredka's bacillary-emulsion antigen, is specific.

2. A positive test indicates, with rare exceptions, the presence of an *active* tuberculous focus somewhere in the body, while a negative test, for biological reasons, does not exclude the diagnosis of tuberculosis.

3. In a certain number of syphilitic sera (11.76 per cent) without clinical evidence of tuberculosis, the complement is fixed in the presence of the tuberculosis antigen. Therefore, in such cases, the diagnosis of tuberculosis must be accepted with caution.

4. Besredka's bacillary-emulsion antigen can be preserved indefinitely.

5. The complement-fixation test in tuberculosis, with Besredka's antigen, is a reliable method of diagnosis in tuberculosis.

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THE COMPLEMENT-FIXATION REACTION IN TUBERCULOSIS WITH KOLMER'S QUANTITATIVE METHOD[1]

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Attempts to apply the complement-fixation reaction to the diagnosis and prognosis of tuberculosis have been numerous, with results that have been variable and, on the whole, disappointing.

It is not to be expected that the test can take the place of a careful study of the disease and the patient. This will never be true of any laboratory procedure in any disease, although there has been some tendency at times, as in the use of the test in syphilis, to throw the entire burden on the laboratory and to demand that it relieve the clinician of the necessity for anything other than the collection of the specimen.

Assuming a positive complement-fixation test in tuberculosis to represent an immunological reaction, indicative of the interaction of an antibody and an antigen, there are various possible explanations for the inconsistent results reported by various observers, partly related, on the one hand, to matters of technique, and, on the other, to factors inherent in both disease and patient.

Among those related to technique, possibly the most important is the antigen. Many have been proposed and probably the most suitable is yet to be found. It seems likely that the best antigen is that which contains the bodies of the bacilli rather than an extract, such as tuberculin; but, whatever the antigen, it seems clear that a potent source of difficulty in analyzing the results has been a failure to recognize to the fullest extent the narrow margin between the antigenic and the anticomplementary doses of those thus far utilized.

This is a factor which must be carefully compensated for, if erroneous results are to be avoided.

The two facts which seem to be well established as regards antigens may be thus stated:

[1] From the laboratories of the Pittsburgh Hospital.

[2] Formerly Director of laboratories, Pittsburgh Hospital.

1. Antigens embodying suspensions of the bodies of the bacilli seem more constant and reliable in their results, though it is not yet definitely shown whether such suspensions are best prepared from living or dead bacilli.

2. Antigens representing extracts, such as tuberculin, are not as delicate, reliable, or as constant in their results as suspensions.

As indicated above, it is quite possible that some of the positive results, recorded as occurring in nontuberculous controls, may have been due to failure to allow, in the adjustment of the test, for the narrow margin between the antigenic and the anticomplementary doses.

Several investigators have called attention to the fact that the complement of certain guinea pigs may fail to react with tuberculous serum, thus necessitating the use of pooled complement serum; and others, among whom may be noted Aronson and Lewis (1) and Upham and Blavais (2), have mentioned the occurrence of positive reactions in the serum of guinea pigs without demonstrable signs of tuberculosis at autopsy. Whether it will be necessary in the future to use only tested complement serum time alone will show.

A possible reason for the failure to obtain a positive reaction in a certain percentage of cases of known tuberculosis is the belated recognition of the fact that a much longer period of primary incubation is required than was needed in the original Wassermann test, and another element of some importance is the necessity for avoiding an excess of complement in the adjustment of the hemolytic system.

The presence of natural hemolysins in the serum to be examined seems, from the work of Rogers (3), to be of no importance. The same observer, however, after investigating the properties of various antigens prepared from a number of acid-fast bacteria other than the tubercle bacillus, concludes that the reaction is not a specific antigen-antibody reaction but a group reaction, and this point seems worthy of further study and elucidation.

Whether the reaction is a group reaction or, as others hold, a specific reaction, it is clear that the reacting substance partakes of the nature of an antibody.

Stimson (4), calling attention to the fact that the mere presence of antibodies cannot be taken as an indication of immunity, because they are not found in individuals who have resisted the disease and because they have been demonstrated to diminish and disappear upon recovery from tuberculosis, prefers to look upon them as an evidence of tissue

reaction to infection with the tubercle bacillus and to call them "reaction bodies." This conception would make the test quite comparable to the complement-fixation test in syphilis, in which disease a positive reaction is an indication of an interaction between the tissues and the spirochetae and a negative reaction simply evidence of the lack of such interaction.

The purpose of the present communication is simply to report, without entering into an exhaustive survey of the subject, the results obtained with the complement-fixation test in a series of 104 cases of tuberculosis, using the quantitative method described by Kolmer (5).

The inception of the study arose from an analysis of the results obtained with this method in syphilis, the report of which has been published elsewhere (6) (7). One of the conclusions resulting from this investigation was that the excellent results obtained with this technique were due, not only to the excellence of the antigen, but in no small measure to the various refinements of technique whereby the amount of foreign protein in the system was reduced to a minimum.

It seemed of interest, therefore, to see what would be the results in tuberculosis by this method and the investigation was, accordingly, begun. The primary purpose was to see in what proportion of known cases a positive reaction would be obtained with the method, rather than to apply it to a large variety of conditions.

An initial difficulty—what species of antigen to use—was solved through the courtesy of Dr. Kolmer who kindly supplied the antigen used throughout the series.

This antigen was prepared by prolonged extraction of the bacilli with lipoid solvents, following which they were dried and thoroughly pulverized. The dried powder was then suspended in water in the proportion of 0.1 gm. to 10 cc., the suspension boiled for one hour and then made isotonic. This boiled and isotonic suspension constituted the antigen, which was then titrated for its anticomplementary value. The method of its preparation will later be published in detail.

The sera were all obtained from patients in the Leech Farm Sanitarium of the City of Pittsburgh and were secured through the coöperation of the Medical Superintendent, Dr. Joseph Shilene, to whom acknowledgement is due. All sera were tested within 48 hours of their receipt after inactivation for 15 minutes at 55°C.

The technique of the tests was in all respects exactly as described by Kolmer, except that the serum doses were those recommended in a subsequent pub-

lication (8). The antigen was used in doses of 0.5 cc., which amount was always one-fourth of the anticomplementary unit. The amboceptor dose was determined by titration, and this amount used in doses of 0.5 cc. for the complement titration, which was performed in the presence of the test dose of antigen just prior to the main test.

Of the 104 cases tested, the sputum was positive for tubercle bacilli in 78 on a single examination; of the 26 cases in which the bacilli were not found prior to the complement-fixation test, 2 were cases of asthma and one was diagnosed as tuberculous enteritis. At the same time the sera were tested for tuberculosis complement fixation, a complement-fixation test for syphilis was also made, this being performed by Kolmer's quantitative method also.

The cases were classified as to type by the extent of the lesions as demonstrated by physical signs, and as to activity by the degree of systemic activity observed. The classification of tuberculosis is a matter upon which few clinicians agree and, until the ideal is reached, one is more or less obliged to accept those in vogue.

The classification furnished by Dr. Shilene was as follows:

Incipient: slight initial lesion in the form of infiltration limited to the apex of one or both lobes or a small part of one lobe; no complications; slight or no constitutional symptoms; expectoration slight or absent; tubercle bacilli present or absent.

Moderately Advanced: no marked impairment of function either local or functional; no serious complications.

Far Advanced: marked impairment of function, local and constitutional; localized consolidation, intense or disseminated areas of softening, or serious complications.

Von Wedel (9) suggests a classification into four types based upon the degree of antibody production as evidenced by the complement-fixation test. This suggestion, while it has much in its favor, cannot be adopted until the test is finally evaluated.

RESULTS OF THE SERIES

The total number of cases in which the blood specimen was accompanied by a positive sputum was 78, but it must be remembered that the sputum reports in a majority of cases represented the results of the first, single examination. It is beyond doubt that a certain number of the negative sputa were later found to be positive; in any event, there was no doubt of the diagnosis in the cases classed as pulmonary tuberculosis.

A negative sputum, moreover, will be a frequent concomitant of the complement-fixation test for tuberculosis if it comes into more or less common use for, even as some are now satisfied with the results of very few sputum examinations, so also will there be some content to throw the entire burden of proof on the complement-fixation tests.

Of the 78 cases with positive sputum, 57 or approximately 61 per cent gave a positive fixation reaction of varying degree. The total number of positive reactions in the entire series was 67 or 64 per cent; 36 or 34 per cent were negative on a single examination.

The results in general may be thus tabulated:

Sputum positive and complement-fixation positive	57 or 54 per cent
Sputum negative and complement-fixation positive	22 or 21 per cent
Sputum positive and complement-fixation test negative	14 or 1.3 per cent
Sputum negative and complement-fixation test positive	10 or 0.9 per cent
Anticomplementary	1 per cent
Total positive complement-fixation reactions	67 or 64 per cent
Total negative complement-fixation reactions	36 or 34 per cent

These results, it must be remembered, represent the results of a single examination of the serum in each instance.

The reactions varied in strength from very strongly positive by the Kolmer scale (fixation in four or all five tubes of the series), to weakly positive (fixation in the first tube only). They were distributed as follows:

Moderately advanced cases:		*Far advanced cases:*	
Very strongly positive	11	Very strongly positive	10
Strongly positive	16	Strongly positive	6
Moderately positive	11	Moderately positive	7
Weakly positive	3	Weakly positive	2

While there was a distinct relation between the degree of activity and the strength of the reaction this, as might have been expected, was markedly modified by the ability of the patient to react.

The cases in which both the sputum examination and the complement-fixation test were negative are of some interest. Two were diagnosed as asthma and noted as without the physical signs of tuberculosis; one was a chronic empyema; one a case of tuberculosis of the spine, far advanced; one practically moribund; one a case of tuberculous enteritis; one an "arrested incipient"; one incipient; three chronic fibroid cases; and the remainder moderately advanced cases of pulmonary tuberculosis in fair clinical condition.

Of the 14 cases with a positive sputum and a negative fixation reaction, 6 were far advanced in type and the remainder moderately advanced cases.

As might have been expected from the reports of other investigators, the results of this small series were not comparable to the results ob-

tained with the complement-fixation test in syphilis. With the method used, however, when obtained the reactions were quite clear-cut, could be definitely measured as to degree, and are not without some encouragement. Cross-fixation with syphilitic antigen was not obtained.

It is quite evident from the results, which are quite comparable to those obtained by others, that circulating antibodies are present in the blood in tuberculosis, and that they may be detected in a definite proportion of cases. It is also evident that their constant detection, while influenced to no small extent by details of technique, is not to be looked for to the same degree as obtains in syphilis, possibly because of the varying antigenic values possible in the two antigens, but largely because of factors inherent in the disease and the individual in whom it exists.

While the presence of circulating antibodies is admitted and demonstrable, it is equally demonstrable that they are neither constantly present nor constantly produced in detectable quantities, facts which markedly influence the clinical value and interpretation of the test.

As always, it is not the test but the interpretation which is of significance.

If we look upon the bodies which react as true immunological antibodies, the occurrence of positive reactions in supposedly nontuberculous controls is readily explained if, as is commonly held, we admit that a large proportion of individuals bear the scars of healed tuberculosis. If, on the other hand, as Stimson suggests, we consider them as reaction bodies, as a measure of the degree of interaction between the tissues and the invading microörganisms, the occurrence of negative reactions in active cases can only be explained by assuming that the body cells are overwhelmed and lie prostrate before the advancing forces of bacilli and are unable to resist and thus produce substances reacting to the complement-fixation test.

Whatever the true conception of the reacting substances, it seems reasonable to suppose that the mechanism concerned with their production is closely allied to that concerned in the production of antibodies. That their presence, as evidenced by a positive reaction, is an evidence of immunity, is untenable; that it is an indication of activity of a tuberculous focus, coupled with an ability of the body to react, seems quite likely.

One of the incidental purposes of the investigation was to determine the suitability of the technique used for the complement-fixation test in tuberculosis.

As a result of the experience with Kolmer's quantitative method in this series it can be said that it is quite suitable for the purpose. The reactions when obtained were quite clear and distinct and, because of the quantitative nature of the method, could be definitely graded as to strength.

As only the one antigen was used, no estimate of its antigenic value as compared with other antigens could be made; that is, it is not possible to state definitely whether sera reacting negatively with this antigen might have been positive to another. In view of the character, strength and distinctness of the reactions obtained, however, it is logical to assume that the negative reactions indicated an absence of reacting substances, rather than any antigenic deficiency on the part of the antigen, and that the same sera would, therefore, have been negative to other antigens also. Whether it exceeds in antigenic value other antigens the series furnishes no evidence for or against.

Considering all the data at hand what is the possible clinical value of the complement-fixation test in tuberculosis?

It is not to be hoped for, as has already been said, that it shall take the place of a careful physical examination supplemented by as many sputum examinations as may be necessary.

It may not be amiss here to note the inadvisability of abandoning the possibility of tuberculosis as a diagnosis because two, four, or a dozen sputum examinations have been negative. As long as there are physical signs suggestive of tuberculosis, sputum examinations should be repeated until either the bacilli are found or the condition can be shown to be non-tuberculous. As an evidence of the necessity for this, recollection brings to mind the memory of a typical case of pulmonary tuberculosis presenting the classical picture of an advanced condition seen in the A. E. F., in which bacilli were only demonstrated in the sputum on the forty-fourth consecutive trial.

In a given case the occurrence of a positive complement-fixation reaction when the sputum is negative, especially if this finding be repeated, would be strong evidence of the presence of an active tuberculous focus, although, as yet, the diagnosis should hardly rest upon this uncorroborated evidence.

The laboratory cannot replace careful clinical study nor scientific acumen. It must always be utilized in conjunction with other methods of study, and the results as a whole must always be weighed in the balance of skill, knowledge and experience.

If it is demanded of the complement-fixation test that it give positive reactions in a large proportion of early cases with lesions too small to detect and with practically no symptoms, the test will prove a disappointment, for in such cases either the tissue-bacillus interaction will be lacking, or of so minor a degree that reacting bodies will only be detected in a small proportion of cases.

To the specialist, adept, well-trained, and well informed in the manifestations of the disease, the test in its present state brings but little.

To the man not so trained and experienced; to the man who, not infrequently, looks upon a case as incipient which, to the specialist, would be at least well advanced; in the case in which the suspicion of tuberculosis exists without the certainty, the test will be of decided value as an aid in diagnosis.

Tuberculosis cannot be ruled out because of a negative complement-fixation reaction, but the occurrence of a positive reaction, especially if repeatedly demonstrated, forms quite strong evidence of the existence of a tuberculous focus, without, however, assigning this as the cause of the symptoms observable. As an aid in prognosis it brings to the specialist, again, very little; to the practitioner at large, when intelligently used, it may be of great assistance. This is particularly true when a quantitative method, such as that devised by Kolmer, is utilized.

For example, in a moderately active case in which the clinical condition is good, the gradual decrease in the strength of the reaction would be good evidence of the lessening of the degree of activity and justification for a temporarily good prognosis; for, of course, a flare-up may occur at any time in any case.

Conversely, if the clinical condition is poor an entirely different construction would be placed upon the lessening or disappearance of the reaction; the patient was probably being overwhelmed and unable to produce reacting substances; or, should such a patient show, at first, a weak reaction, the strength of which later increases, the prognosis would be guarded until the final trend of the reaction was established.

In other words, the value of the complement-fixation test in tuberculosis depends entirely upon the degree of intelligence and clinical acumen with which it is utilized and, particularly, interpreted in correlation with the clinical data. Under such circumstances it can be of marked diagnostic and prognostic value to the general practitioner, but it must always be intelligently interpreted.

In incipient cases it will be of relatively little value for diagnosis; in moderately and far advanced cases its greatest value will be as an aid to prognosis.

It is undoubtedly a procedure worthy of more extended utilization.

SUMMARY

The results of complement-fixation tests upon 104 cases of tuberculosis are reported and the findings discussed.

CONCLUSIONS

1. The quantitative method of complement fixation devised by Kolmer is well adapted for use in tuberculosis.
2. When properly interpreted in conjunction with the clinical data, it may be of decided value as an aid in diagnosis and prognosis.
3. Cross-fixation of syphilitic antigen by tuberculous sera does not occur.
4. The complement-fixation reaction in tuberculosis is worthy of more extended clinical use.

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FURTHER STUDIES ON THE COMPLEMENT-FIXATION TEST FOR TUBERCULOSIS

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Among recent writers, many, such as Renon (1), Petroff (2), Upham and Blavais (3), Punch (4), Heckmann (5), von Wedel (6), Watkins and Boynton (7), Cook (8) and Ichok (9), speak highly of the value of the complement-fixation test for the diagnosis of tuberculosis. On the other hand, some, such as Rogers (10), Johns (11) and Buddy (12), are somewhat sceptical about the clinical value of the test. Editorially, the *Journal of the American Medical Association* stated some time ago that the complement-fixation test in tuberculosis is still in the experimental stage and that it is not to be considered even fairly efficient, as compared with the Wassermann test in syphilis.

It is true that the test is still in the experimental stage, but the diversity of opinions and findings seems to be due to the difference in antigens, technique and immunological interpretation of the results. For instance, early in the course of this work, it was noticed that antigens of alcoholic extract and aqueous extract of tubercle bacilli gave lower percentages of positive reactions than antigens of emulsoid or suspensoid of whole tubercle bacilli; also that Petroff's glycerine antigen (13) was most dependable. It was further found that serums 48 hours old gave higher percentages of positive reactions than the same serums when fresh (with some antigens). It was also noticed that some actively tuberculous patients, who at first had given negative reactions, gave positive reactions after a course of complete rest or continued negative reactions with extension of the disease. Quiescent patients with negative tests gave positive tests after a few days of exercise.

The following findings are presented in an attempt to substantiate the value of this test, with the hope that it will stimulate further interest along these lines.

SERIES A

The following is a study of 980 mixed patients, made at the Cleveland City Hospital and in the department of pathology of Western Reserve Medical School:

Reagents used: (1) *Antigens:* (a) emulsoid of human tubercle bacillus of several strains in normal saline solution, for tuberculosis; (b) alcoholic extract of beef heart muscle, for syphilis (14). (2) *Patients' serums* were inactivated for 30 minutes at 57°C. (3) *Complement:* 1 to 15 dilution of fresh guinea pig serum in normal saline solution. (4) *Amboceptor:* an antisheep hemolytic amboceptor, the titre of which was 1 to 10,000. (5) *Cell suspension:* a 5 per cent dilution of sheep's blood, washed six times in normal saline solution: 0.5 cc. was used as a unit.

System: A modified 3-tube system of Citron was used throughout the experiment. Five test tubes were used: one for the serum control, a second and a third for syphilis, and a fourth and a fifth for tuberculosis. The first tube contained 0.1 cc. of serum, 1.5 units of complement, but no antigen; the second, 0.05 cc. of serum, 0.05 cc. of syphilitic antigen and 1.5 units of complement; the third, 0.1 cc. of serum, 0.1 cc. of syphilitic antigen and 1.5 units of complement. The fourth and fifth tubes were for tuberculosis, the relation of serum and antigen being exactly the same as in the syphilitic tubes, only tuberculous antigen was used (see table 1).

TABLE 1

TUBES	I	II	III	IV	V	VI	VII
Serum in cc.	0.1	0.05	0.1	0.05	0.1	0	0
Syphilitic antigen in cc.	0	0.05	0.1	0	0	0.2	0
Tuberculosis antigen in cc.	0	0	0	0.05	0.1	0	0.2
Complement units	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Salt solution to make cc.	0.5	0.5	0.5	0.5	0.5	0.5	0.5

These were incubated 4 hours at 8 to 10°C. or one hour at 37°C. One cubic centimetre of sensitized sheep's cells (0.5 cc. of suspension of sheep's cells plus 0.5 cc. of amboceptor) was added to each tube, mixed well and incubated 30 minutes at 37°C. It was then read. We found it best to incubate 10 minutes at 57°C. as soon as the control tubes were hemolized. Then the reading may be taken at any time.

Physical examinations of the patients in this series were checked up by the resident physicians in charge of each department. As we could not take X-ray pictures of the chests of all the patients, the diagnosis of pulmonary tuberculosis was not so complete as in series B.

Of 980 patients examined, there were 114 with positive complement-fixation tests and 252 with positive Wassermann tests. Of 728 Wassermann-negative serums, there were 74 positive complement-fixation tests, and of 252 Wassermann-positive serums there were 40 positive complement-fixation tests. Of the 114 positive complement-fixation tests, 44 were from 53 clinically tuberculous patients; 43 from 71 clinically suspected tuberculous and 27 from 856 clinically nontuberculous patients. These 27 positives from the nontuberculous were distributed as follows: 14 from 638 uncomplicated nontuberculous patients; 9 from 175 syphilitic patients, and 4 from 43 suspected syphilitic patients.

The higher percentage of positive complement-fixation tests among the syphilitic but nontuberculous patients, offered ground for suspicion that strong Wassermann-positive serums might be giving positive complement-fixation tests with the lipoid of tuberculosis antigen. Great effort was made to obtain as many autopsies as possible, in order to check up our serological findings, but unfortunately we obtained only 14 such permissions which are too few to be of much value. These, however, give some idea as to the questionable nature of positive complement-fixation tests among strongly positive Wassermann serums and the accuracy of clinical diagnosis.

Of these 14 autopsies, as shown in table 2, 8 giving positive complement-fixation tests with negative Wassermann tests, all showed definite active tuberculosis. Of 6 giving positive complement-fixation tests with positive Wassermann tests, 4 showed definite active tuberculosis, one questionable active tuberculosis, and one no evidence of active tuberculosis.

SERIES B

This comprised a study of 208 patients made at the Trudeau Sanatorium Clinical and Research Laboratory from September, 1921, to March, 1922. The reagents and technique were the same as in series A, except that Petroff's antigen was used for tuberculosis. In this series the physical examination of the patients was made by the medical staff with the aid of the department of roentgenology and the serological examination was made independently in the research laboratory. The findings are given in table 3.

Thus, 80.4 per cent of clinically tuberculous patients gave positive complement-fixation tests, while only 46 per cent of them showed tubercle bacilli in their sputa. Of 80 positive sputa, 68 were among patients

TABLE 2

NUMBER	CLINICAL DIAGNOSIS		WASSERMANN TEST	COMPLEMENT-FIXATION TEST	AUTOPSY FINDINGS
	Tuberculosis	Syphilis			
3	±	0	0	+++	Tuberculosis of spine with old pulmonary tuberculosis
7	0	+	++++	++++	Pulmonary tuberculosis left upper lobe
12	+	0	0	+++	Disseminated pulmonary tuberculosis
16	0	+	++++	++	Tuberculous bronchoadenitis
24	+	+	++++	++++	Tuberculous meningitis with tuberculous lymph nodes
26	+	0	0	++	Tuberculous pneumonia
28	0	+	++++	+	Absence of tuberculous lesions
35	+	0	0	+++	Fibroid pulmonary tuberculosis
67	±	0	0	++	Caseous pulmonary tuberculosis
81	0	±	++++	++++	Tuberculous bronchopneumonia
88	+	0	0	++	Caseous tuberculous adenitis
104	+	±	0	++	Ulcerative pulmonary tuberculosis
112	0	+	++++	+++	Fibroid pulmonary tuberculosis
113	+	0	0	+++	Miliary tuberculosis

Summary

CLINICAL DIAGNOSIS	NUMBER OF CASES	COMPLEMENT-FIXATION TEST			WASSERMANN TEST		
		Positive	Negative	Positive	Positive	Negative	Positive
				per cent			*per cent*
Tuberculous nonsyphilitic	46	37	9	80.4	1	45	2.1
Suspected tuberculosis, nonsyphilitic	40	25	15	62.5	1	39	2.5
Nontuberculous, nonsyphilitic	638	14	624	2.2	18	620	2.8
Tuberculous, syphilitic	4	4	0	100	4	0	100
Suspected tuberculosis, syphilitic	22	15	7	68.2	21	1	95.4
Nontuberculous, syphilitic	175	9	166	5.1	169	6	96.5
Tuberculous, suspected syphilis	3	3	0	100	2	1	66.6
Suspected tuberculosis, suspected syphilis	9	3	6	33.3	7	2	77.7
Nontuberculous, suspected syphilis	43	4	39	9.3	29	14	67.4
Total	980	114	866	11.6	252	728	25.7

with positive complement-fixation tests, while 12 were among patients with negative complement-fixation tests.

Of 10 unwarranted cases 2 gave positive tests. Of 10 suspected cases 3 gave positive tests. One of them, no. 5843, had a history of hemoptysis; but as she had no physical signs and symptoms she was classified as a suspected case. She had given a positive test at the time of her admission. Later, during her stay in the sanatorium, she lost some weight and was feeling tired, and at the same time her blood test became negative. A few weeks later she had a frank hemoptysis, accompanied by other clinical symptoms, and a definite diagnosis of tuberculosis was made. At the time of her discharge, several weeks later, her serum gave a strongly positive test. Two others, nos. 5804 and 5830, also had a history of hemoptysis with no other clinical symp-

TABLE 3

Summary of Series B

NUMBER EXAMINED	CLINICAL DIAGNOSIS	LABORATORY DIAGNOSIS					
		Positives		Negatives		Percentages of Positives	
		Complement fixation	Sputum	Complement fixation	Sputum	Complement fixation	Sputum
14	Nontuberculous	0	0	14	14	0	0
10	Unwarranted	2	0	8	10	20	0
10	Suspected	3	0	7	10	30	0
19	Minimal	8	5	11	14	42.1	26.3
138	Moderately advanced	116	63	22	75	84.1	45.7
17	Far advanced	16	12	1	5	94.0	70.6
174	Total tuberculous	140	80	34	94	80.4	46.0

toms. Of 19 minimal cases 8 gave positive complement-fixation tests. All these positive cases were doing well, while the negative cases were either those which had been quiescent for some time or those which were doing poorly clinically. Patients nos. 5782, 5723, 5717, 5790 and 5698 were quiescent, while nos. 5671, 5853 and 5724 were doing poorly. Patients nos. 5807 and 5821 were interesting cases. The former had positive sputum all the time of his stay and yet very few physical signs, and his blood tests were repeatedly negative. He apparently felt well, yet there were more definite physical signs at the time of discharge than at the time of admission. The latter had profuse expectoration, often streaked with blood, and repeated sputum examinations had been negative. Repeated blood tests were also negative and the physical

signs were increasing, yet the patient was apparently feeling well. Of 138 moderately advanced cases 117 gave positive tests. Twenty-one who had negative complement-fixation tests were either those who had been quiescent for some time or who did poorly clinically. Those cases which were doing poorly were nos. 5866, 5865, 5890, 5852, 5894, 5813 and 5886. Patient no. 5886 was one of those borderline cases who was feeling tired with occasional fever. Patient no. 5865 had bad teeth and streaked sputum constantly. Patient no. 5866 appeared to be well, but ran a little fever and had frequent hemoptyses. Patient no. 5890 had been in bed frequently and the disease was extending. Patient no. 5852 had several hemoptyses and was feeling weak. Patient no. 5894 was in bed most of the time with fever; he began to show some pus and tubercle bacilli in the urine, and a diagnosis of tuberculosis of the prostate, and possibly of the kidney, was made. Patient no. 5813 was doing fairly well, but had slight fever. Patient no. 5805 had several hemoptyses; yet the last X-ray plates showed slight improvement over the admission plates; probably absorption of blood had taken place; the complement-fixation test remained negative. Of 17 far advanced cases 16 gave positive tests and most of them were doing well, while one with negative test, no. 5827, had intestinal complications and was doing poorly.

It must be remembered here that not all the cases giving positive fixation tests were improving. There were many with positive tests showing extension of the disease; nos. 5802 and 5849 were good examples. At the same time there were some with negative tests and showing improvement.

Some laboratory workers and many clinicians have stated that the complement-fixation test does not signify the presence of any immunity to tuberculosis, inasmuch as patients with both positive and negative tests seem to become better or worse regardless of the test. But this seems to us to be an erroneous interpretation, for (1) the circulatory antibody titre in the patient's blood is not constant and (2) after activity, if the system reacts, the titre is higher. As time passes a quiescent state occurs and the blood titre becomes low and later it may become negative. If nothing happens the tuberculosis may develop into the so called "arrested condition"; but, if the patient now takes cold or undergoes excessive mental and physical exhaustion, a relapse may take place and the blood become positive again. Such a cycle of events may take place many times in one patient. Some cases remained negative or positive during their residence of six months in the sanatorium.

From the foregoing, it appears that the complement-fixation test in tuberculosis compares favorably with the Wassermann test in syphilis for diagnostic purposes. It resulted in 42 per cent of positives in minimal, 84 per cent in moderately advanced and 94 per cent in far advanced cases, averaging 80.5 per cent in the total tuberculous patients examined. At the same time, there were only 26.3 per cent of positive sputa among the minimal, 45 per cent among the moderately advanced and 70.6 per cent among far advanced, averaging 46 per cent in the total tuberculous examined.

SUMMARY

1. Positive complement-fixation tests among strongly positive Wassermann serums were not always dependable when emulsoid of tubercle bacillus was used as antigen.

2. Syphilitic antigen did not fix complement in tuberculous sera.

3. The complement-fixation test in tuberculosis, for diagnosis, compares favorably with the Wassermann test in syphilis, when proper antigens and technique are employed.

4. The positive complement-fixation test is very useful in the diagnosis of tuberculosis, especially in cases in which clinical symptoms and physical signs are indefinite; but a negative reaction does not exclude tuberculosis just as a negative Wassermann does not exclude syphilis.

5. Other factors being equal, active tuberculosis patients with positive tests seem to do better clinically than those with negative tests.

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A STUDY OF THE ANTIGENIC PROPERTIES OF BACTERIA GIVING COMPLEMENT FIXATION WITH TUBERCULOUS SERA[1]

L. DIENES AND L. BALAS

In a previous article Dienes and Schoenheit (1) showed that through the absorption experiment of Castellani we are able to demonstrate that, in the sera of rabbits treated with tubercle bacilli, the antibodies reacting with the alcohol extract of tubercle bacilli are different from the antibodies reacting with the proteins of the bacilli. It is known that the emulsion and alcoholic extract of bacteria other than tubercle bacilli can give complement fixation with tuberculous sera. From the very extensive literature we mention, as illustrations, only two recent works. Schlossberger and Pfannenstiel (2), in an extensive study of cross-complement fixation between sera and strains of the acid-fast group, could not find any constant difference between the tuberculous and the saphrophytic strains. Nègre and Boquet (3), using Calmette's method, estimated the antigenic value of the alcoholic extracts of different bacilli, and found the extract of diphtheria bacilli as potent as the extract of human and bovine strains of tubercle bacilli, and the extracts of acid-fast saphrophytes nearly half as potent.

For the further study of the antigenic properties of the alcohol extracts of tubercle bacilli it seemed important to us to examine the behavior, in the absorption experiment, of the emulsion and extracts of the bacilli giving complement fixation with tuberculous sera. The absorption experiment would give an answer to us if the antigens examined are as closely similar as our methods allow our determining it, and permits us to distinguish between the close and more distant relationships. At the same time, our observations contributed to the study of the serological relationships between tubercle bacilli and the so called acid-fast saphrophytes.

We tested several tuberculous sera with the emulsion of different strains of tubercle bacilli, in order to obtain information as to whether

[1] From the Von Ruck Research Laboratory for Tuberculosis, Asheville, North Carolina.

the strains all belong to the same serological group. We tested the same sera with the emulsion and lipoid extracts of some so called acid-fast saphrophytic strains and of the diphtheria bacillus. We used, from the acid-fast group, Moeller's grass bacillus, the *Bacillus phlei* and the *Bacillus smegmatis*, for which we are indebted to Professor A. Kendall of Chicago. For controls we used the alcoholic extracts of staphylococcus and *Bacillus subtilis*, alcoholic guinea-pig kidney extract (which contains the so called heterogenetic antigen) and noncholesterinized beef extract used for the Wassermann reaction. The alcoholic extracts were obtained in the same way as previously described for the tuberculous extracts. First we extracted the dried bacilli with ether, then with alcohol. With the diphtheria and subtilis bacilli and staphylococci we have also used the method given by Boquet and Nègre (4) of alcoholic extraction after acetone extraction. The content of the extract in dried material is given in the corresponding tables.

The technique used for the absorption experiment and for complement fixation was the same as previously described. We have to add to this that some sera are sensitive to the alcohol contained in the extracts, and that the control serum has to contain the same amount of alcohol and has to be filtered in the same way as the serum under examination.

Tables 1 to 5 embody the experimental material. In the literature we have found no information as to whether the different strains of tubercle bacilli belong to the same serological group, according to either agglutination or complement fixation. We found mentioned the absorption experiment with tubercle bacilli in one of the latest publications of Lewis and Aronson (5), containing no details. According to them, bovine and human strains are alike, the avian differing from them. The few strains we examined belong in the same serological group (table 1). Among them are some bovine strains (bovine 3, bovine A), and some of them are old laboratory strains (H37, HA, H597 and the bovine strains); others have been quite recently isolated (D and G). The effect of the alcoholic extracts of the acid-fast saphrophytes is similar to the effect of the alcoholic extract of tubercle bacilli; the absorption experiment shows no difference between them (table 2). Contrary to this, the extract obtained in the same manner from the diphtheria bacillus, staphylococci and the different organ extracts have no specific reaction with the antibodies of the tuberculous serum. As is shown in table 2, the acid-fast saphrophytes do not influence the antibodies of the tuberculous serum that are connected with the proteins of the bacilli, and the proteins of the

acid-fast saphrophytes cannot absorb any antibody from the tuberculous serum (table 3).

According to table 5 a tuberculous serum devoid of the lipoid antibodies gives complement fixation with the emulsion of acid-fast saphrophytes and the watery extract of the saphrophytes gives fixation with it. These facts show that the proteins of the saphrophytic acid-fasts have some common reaction with the proteins of tubercle bacilli; but this similarity

TABLE 1

	CHECKING OF THE FILTRATE WITHOUT ANTIGEN	TITRE OF THE FILTRATE WITH BACILLARY EMULSION OF TUBERCLE BACILLUS STRAIN HD
Rabbit serum 50, 3 cc. of the dilution 1:10 treated with 0.3 gm. wet bacillary mass of the tubercle bacillus culture H37, 3 hours in the incubator, then ordinary temperature and filtered	1:5 ±−−−	1:10 ++−−
The same with the strain HA	1:5 ++++ 1:10 ++−−	1:10 +++−
The same with the strain HWh	1:10 ++++	1:20 ++++
The same with the strain H597 (only 0.12 gm. wet bacillary mass used)	1:10 ++++	1:20 ++++
The same with the strain HG (only 0.12 gm. wet bacillary mass used)	1:20 ++++	1:40 ++++
The same with the strain Bovine 3	1:5 +−−−	1:10 ++−−
The same with the strain Bovine A	1:10 ++++	1:20 ++++
The same with the strain HD (with which the serum was obtained)	1:10 −−−−	1:10 −−−−
Untreated serum 50	1:10 +−−−	1:320 ++++

does not go further, as is shown by the absorption experiment as we often find it with closely related groups of bacilli.

We made some experiments to judge whether we can produce antibodies against the lipoid extracts of bacteria not belonging to the acid-fast groups. We succeeded with the diphtheria bacillus and did not succeed with the staphylococci. We injected intravenously, at weekly intervals, 1 to 2 cgm. of wet bacillary material, suspended in 0.5 per cent

phenol saline solution. The titre of the serum of the rabbit injected with staphylococci was 1 to 1280, without showing a trace of checking with the alcohol extract made directly from the dried bacilli or made after ether and after acetone extraction. In tables 6 and 7 are the observations relating to the diphtheria serum. The serum gives a potent fixation, with both the tuberculous emulsion and the tuberculous alcoholic extract. The absorption experiment with the emulsion of diphtheria bacilli and with the alcoholic extract of them has given the same result as we have found with the tuberculous sera. Unfortunately, we could not get reliable experiments with the tuberculous alcoholic extract due to the low titre and high checking in itself of the serum.

Our knowledge about the alcohol-soluble substances, which have antigenic effect *in vivo* or *in vitro*, is quite recent, and we are not well instructed about the occurrence of them and the relationship existing between them. The experience with heterogenetic antigens, which shows much similarity to the specific lipoids found in the acid-fast bacilli, shows that the specific lipoids, contrary to the specific proteins, are not bound to the animal species but are distributed indifferently of the relationships between the species. By the Wassermann reaction, which probably belongs to the same group of phenomena, we find the antigen likewise distributed quite extensively in the animal and probably in the vegetable kingdom. Besides these two, the occurrence of alcohol-soluble antibodies was observed with tenia, acid-fast bacilli and diphtheria bacilli. The findings of Strubell (6), relating to the staphylococci, seem not to be verified by the following researches (7), as we have to wait for the confirmation of the interesting finding of Schlemmer (8) that the origin of bacteriolysins of typhoid bacilli is in the lipoids.

It was shown by K. Meyer (9) that the antigenic properties of the heterogenetic antigen, the tenia extract and the extract of acid-fast bacilli are different. But we have no information as to whether the distribution of the other lipoid antigens is like that of the heterogenetic antigen, that is not bound to natural species. Our observations on the occurrence of the same lipoid antigens connected with different protein antigens can be interpreted in favor of the idea that with the bacilli they also follow the distribution of the heterogenetic antigen. But it is quite likely, on the other hand, that the occurrence of the same partial antigen with different and closely related bacterial species belongs to the category of phenomena lately described and studied with the agglutinins by E. Weil (10) and his associates; that is, that agglutinins which can be

TABLE 2

	CHECKING OF THE FILTRATE WITHOUT ANTIGEN	TITRE OF THE FILTRATE WITH THE STRAIN USED FOR ABSORPTION	TITRE OF THE FILTRATE WITH BACILLARY EMULSION OF STRAIN HD	TITRE OF THE FILTRATE WITH THE ALCOHOL EXTRACT OF STRAIN HD
3 cc. of dilution 1:10 of serum 9, mixed with 0.12 gm. wet bacillary mass of Grass bacillus Moelleri, incubated over night and filtered	1:5 ++++	1:10 ++++	1:320 ++++	1:80 ++−−
The same; only twice as much bacillary mass added in two portions	1:20 ++−−	1:20 ++++	1:320 ++++	
The same with *Bacterium phlei* (0.12 gm.)	1:5 −−−−	1:10 −−−−	1:320 +++−	1:10 −−−−
The same with *Bac. smegmatis*	1:5 ++++	1:10 ++++	1:320 ++++	1:10 ++++
Serum 9, dilution 1:10, mixed with equal amount of dilution 1:5 of alcohol extract of Grass bacillus Moelleri, incubated over night and filtered (1 cc. of alc. extr. contains 0.010 gm. dry material)	1:10 ++−−	1:10 ++++	1:320 ++++ 1:640 +−−−	1:10 ++++
The same with alc. extract *Bac. phlei* (1 cc. = 0.0041 gm.)	1:5 +−−−	1:10 ++−−	1:320 ++++ 1:640 ++−−	1:10 ++++
The same with alc. extract *Bac. smegmatis* (1 cc. = 0.0031 gm.)	1:10 ++++	1:10 ++++	1:320 ++++ 1:640 ++−−	1:10 ++++ 1:20 ++−−
The same with alc. extract of staphylococci (1 cc. = 0.0055 gm.)	1:10 ++++			1:80 ++++
Serum 50, 1 cc. of dilution 1:10, treated with 0.025 gm. dry (around 0.3 gm. wet) diphtheria bacilli, incubated over night, filtered	1:10 −−−−		1:160 ++++	
Serum 95, dilution 1:10, mixed with alc. extract *Bac. diphtheriae*, incubated over night and filtered (1 cc. = 0.0084 gm.)	1:10 ±−−−			1:80 ++−−

Serum 9, dilution 1:10, mixed with alc. beef heart extract, etc.	1:20 ++++			1:80 ++++ 1:160 ++−−
Serum 9, dilution 1:10, mixed with alc. guinea-pig kidney extract, 1:5, etc.	1:5 ++++			1:80 ++++
Serum 50, dilution 1:10, mixed with 1 per cent lecithin solution, 1:5, etc.	1:20 +−−−			1:80 +++−
Serum 9, untreated	1:5 +−−−		1:320 ++++ 1:640 ++−−	1:80 ++++
Serum 50, untreated	1:5 +−−−		1:320 ++++	1:80 ++++
Serum 95, untreated	1:10 ++++			1:80 ++−−

TABLE 3

	CHECKING OF THE FILTRATE WITHOUT ANTIGEN	TITRE OF THE FILTRATE WITH BACILLARY EMULSION, TUBERCLE BACILLUS H597
2 cc. of dilution 1:100 of the serum 81, mixed with protein precipitate of watery extract *Bac. phlei*, incubated over night and filtered	1:100 +++−	1:400 ++++
The same with the precipitate of watery extract of tubercle bacilli	1:50 −−−−	1:100 −−−−
Serum 81, in dilution 1:100, incubated over night and filtered	1:50 −−−−	1:400 ++++ 1:800 +−−−

TABLE 4

Complement fixation obtained with the acid-fast saprophytes, control bacteria and organ extracts

SERUM USED	THE STRAINS FROM WHICH THE ANTIGENS WERE PREPARED	TITRE WITH THE BACILLARY EMULSION	TITRE WITH THE ALCOHOL EXTRACT
Serum 9	*Bac. phlei*	1:80 ++++ (Titre with the watery extract *bac. phlei* 1:80 ++++ 1:160 ++−−)	1:80 ++++
	Bac. Moelleri	1:80 ++++	1:40 ++++
	Bac. smegmatis	1:80 ++−−	1:10 ++++
Serum 50	*Bac. diphtheriae*	1:80 ++++	1:20 ++++
Serum 81	*Bac. diphtheriae*	1:40 ++−−	1:40 ++−−
Serum 9	*Bac. tuberc.*	1:320 ++++ 1:640 ++−−	1:80 ++++
Serum 50	*Bac. tuberc.*	1:320 ++++	1:80 ++++
Serum 81	*Bac. tuberc.*	1:2400 ++−−	1:2400 ++−−

The emulsion and alcohol extract of staphylococci, *bac. subtilis*, the alcohol extract of beef heart, guinea-pig kidney, 1 per cent solution of lecithin, did not give positive reactions.

TABLE 5

	COMPLEMENT FIXATION WITH SERUM 9 DEVOID OF LIPOID ANTIBODIES
Bacillary emulsion of *Bac. phlei*	1:80 ++++ 1:160 ++−−
Bacillary emulsion of *Bac. Moelleri*	1:80 ++++ 1:160 ++−−
Bacillary emulsion of *Bac. smegmatis*	1:80 ++++ 1:160 ++−−

TABLE 6

	TITRE WITH SERUM 97 OBTAINED BY INJECTING A RABBIT WITH DIPHTHERIA BACILLI
Diphtheria bacillary emulsion	1:80 ++++ 1:160 ++−−
Diphtheria bacillus alcohol extract	1:40 ++++
Tubercle bacillus H597 bacillary emulsion	1:40 ++++
Tubercle bacillus H597 alcohol extract	1:40 ++++

TABLE 7

	CHECKING OF THE FILTRATE WITHOUT ANTIGEN	TITRE OF THE FILTRATE WITH DIPHTHERIA BACILLARY EMULSION	TITRE OF THE FILTRATE WITH BACILLUS DIPHTHERIAE ALCOHOL EXTRACT
Serum 97, 2 cc. of dilution 1:10, mixed with 0.025 gm. dry diphtheria bacilli, incubated over night and filtered	1:10 +−−−	1:10 ++++ 1:20 ±−−−	1:20 −−−−
The same with tubercle bacilli H597	1:10 ++++	1:40 ++++	1:20 ++++
Control serum, staying over night in incubator and filtered	1:20 ±−−−	1:40 ++++ 1:80 ++−−	1:40 ++++ 1:80 +−−−
Serum 97, in dilution 1:10, mixed with equal amounts of alcoholic extract of *bac. diphtheriae* 1:5, incubated and filtered	1:10 ++++ 1:20 +−−−	1:40 ++++ 1:80 +−−−	1:20 ++−−
Control serum staying with 10 per cent alcohol and filtered	1:5 ++−−	1:40 ++++ 1:80 ++−−	1:20 ++−−

distinguished from the main agglutinins through the aspect of agglutination and through the difference in the resistance of the agglutinogens are much more widely distributed by the related species than are the main agglutinins. The recent observation of Avery (11) on the pneumococci shows that besides the type specific capsulary substances all types have a common precipitable substance, probably the body substance of the cocci. The observation that the alcohol extract of the diphtheria bacilli, contrary to the weak reaction which they give with the tuberculous sera, does not absorb the lipoid antibody from them, suggests that one should not draw any conclusions from the occurrence of the same lipoid antigens with all acid-fast bacilli for the distribution of the lipoid antibodies, but should see in them only a sign of close relationship between the bacilli.

The behavior of the diphtheria extract shows, besides, that with the alcoholic antigen we can find close and more distant relationships.

SUMMARY

In a small series (eight strains) we have found that the strains of tubercle bacilli belong, according to absorption experiment, to the same serological group. Three strains of acid-fast saphrophytic bacilli (Moeller's grass bacillus, *Bacillus phlei*, *Bacillus smegmatis*) in the absorption experiment have not influenced the tuberculous serum.

The alcoholic extracts of the same saprophytic strains in the absorption experiment are similar to the extract of tubercle bacilli. They absorb all antibodies with lipoid affinity from the sera. The alcoholic extracts of diphtheria bacilli, staphylococci and different organ extracts and lecithin suspension have not influenced, in the absorption experiment, the lipoid antibodies of tuberculous sera.

The serum obtained with diphtheria bacilli in rabbits shows the presence of antibodies against the alcoholic extract of diphtheria bacilli, and these antibodies behave, in the absorption experiment with the alcoholic extract of diphtheria bacilli, like the antibodies of the tuberculous sera with the alcoholic extracts of tubercle bacilli.

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CONDITIONS INFLUENCING THE PRODUCTION OF ANTIBODIES AGAINST THE ALCOHOL EXTRACT OF TUBERCLE BACILLI[1]

L. DIENES AND L. BALAS

In the course of our study of the antibodies against the alcohol extract of tubercle bacilli, we made several attempts to examine the conditions which influence their production. We started from different viewpoints. We observed, by control experiments, whether small amounts of tubercle bacilli, which can be eventually present in unfiltered (porcelain or Berkefeld) extracts, can influence the production of antibodies, that is, that small amounts of tubercle bacilli produce, compared to the antibodies against the whole bacilli, relatively less alcoholic-extract antibodies than larger amounts of bacilli. Then we observed that we get relatively and absolutely more antibodies against the alcohol extract with one of our strains (H597). As this is a fast growing old laboratory strain we investigated what effect the age of the strain and also the age of the culture used may have. Following the observation of Landsteiner (1), concerning the heterogenetic antigen, that the admixture of proteins makes them active *in vivo*, we tried out the effect of the mixture of alcohol and watery extract. Finally, we tried to determine whether long and thorough extraction of the bacilli with ether and alcohol, at ordinary temperature, influences the production of lipoid antibodies. Unfortunately, our findings do not allow us to arrive at any conclusion as to the pathological significance of the appearance of large amounts of lipoid antibodies in the serum of human patients.

It would be useless to present our protocols relating to the age of the strain and of the culture which, according to our experiments (with 12 rabbits), have no influence on the production of antibodies. The titre of lipoid antibodies, after injecting intravenously 1 cgm. of wet bacilli into rabbits, is nearly one-fourth of the titre with the bacillary emulsion. The above mentioned strain (H597) gives sera with which the titres of the two antibodies approximate each other. Later, we

[1] From the Von Ruck Research Laboratory for Tuberculosis, Asheville, North Carolina.

shall return to one serum obtained with this strain. The titre of the two kinds of antibodies is lowered parallel after the last injection.

We found some connection between the relative amount of lipoid antibodies and the amount of bacillary material injected. Table 1 contains our observations. On injecting 1 mgm. of wet bacilli the titre of the alcohol-extract antibodies rises slowly, and represents only one-sixteenth to one-thirty-second of the titre of antibodies against the whole bacilli. After injecting large amounts (3 and 10 mgm.) they rise rapidly, and reach one-quarter to one-half the titre of the serum. Taking into account the small number of experimental animals we shall have to draw our conclusions with some reserve.

Table 2 summarizes the experiment relating to the mixed administration of watery and alcohol extracts. It shows clearly that, under the conditions with which we were working, the mixture was less effective than the constituents given separately. With the alcohol extract alone we got fairly good results. The very high titres of serum 52 and the sera 61 and 44, obtained with the watery extract, confirm our previous findings that the watery extract alone is not able to produce alcohol-extract antibodies. Serum V, produced with bacilli as thoroughly extracted as possible, at ordinary temperature, with ether and alcohol, contained unchanged amounts of antibodies against the alcohol extract.

In the course of our work we have had many occasions to confirm the conclusion reached by Dienes and Schoenheit (2) concerning the lipoid antibodies. We met, however, one serum which makes it necessary to make some additional remarks. The serum 81, obtained as described in table 1 with the strain H597, in the absorption experiment with the alcohol extract, was different from the other sera. The titre after absorption was lessened, not only for the alcohol-extract antibodies, but for the bacillary emulsion as well. For instance, in one experiment, treated in the dilution 1 to 100 with the emulsion 1 to 5 of the alcohol extract of strain H597, the filtrate has shown no fixation with the alcohol extract and only 1 to 200 with the bacillary emulsion (original titre, 1 to 2400), while the control serum, mixed with alcohol and filtered, was not changed at all. Contrary to this, the treatment with four times as large an amount of alcohol extract has not influenced at all the antibodies against the bacillary emulsion of serum 50 or 9. The serum 81 was exactly so influenced with the alcohol extracts of acid-fast saphrophytes, as with the extracts of tubercle bacilli. We examined 7 rabbits' sera obtained with the bacillary emulsion. Two of them,

TABLE 1

	TITRE ONE WEEK AFTER SECOND INJECTION		TITRE ONE WEEK AFTER THIRD INJECTION	
	With bacillary emulsion	With alcohol extract	With bacillary emulsion	With alcohol extract
Serum 49, rabbit injected with 1 mgm. wet culture of tubercle bacilli HD	1:640 ++++	1:40 ++−− (Serum control 1:20 ++−−)	1:320 ++++	1:40 ++++
Serum 50, rabbit injected like rabbit 49	1:640 ++++	1:20 ++++	1:320 ++++	1:20 ++++
Serum 87, rabbit injected with 3 mgm. wet culture HD			1:320 ++++	1:80 ++++
Serum 88 like serum 87			1:160 ++++	1:80 ++++
Serum 82, rabbit injected with 1 mgm. wet culture H597	1:320 ++++	1:20 ++++		
Serum 81, rabbit injected with 10 mgm. wet culture H597	1:640 ++++	1:320 ++++		
Serum 76 like serum 81	1:160 ++++	1:80 ++++		

besides the serum 81, were obtained with the strain H597, as was serum 81, and we did not find this behavior of antibodies except with serum 81. This observation shows that the affinities of the antibodies to the alcohol

TABLE 2

	TITRE WITH BACILLARY EMULSION OF TUBERCLE BACILLI	TITRE WITH ALCOHOL EXTRACT OF TUBERCLE BACILLI
Serum 52, 7 injections of watery extract of HD (dry material injected, 0.25 gm.)	1:1280 ++++	1:20 ++++ (Serum control 1:10 ++−−)
Serum 44, the same as 52	1:160 ++++	1:20 ++++ (Serum control 1:10 ++−−)
Serum 61, 4 injections of watery extract of HD (dry material injected, 0.145 gm.)	1:320 ++−−	1:10 −−−−−−
Serum 41, 7 injections of watery and alcohol extract of HD mixed (dry material injected, watery extract 0.250 gm., alcohol extract 0.012 gm.)	1:80 ++−−	1:10 −−−−
Serum 42, 6 injections of watery extract and alcohol extract of HD mixed (dry material, water extract 0.216 gm., alcohol extract 0.010 gm.)	1:80 ++++	1:20 ++++ (Serum control 1:10 ++++)
Serum 91, 5 injections of water and alcohol extract of H597 mixed (dry material watery extract 0.186 gm., alcohol extract 0.0116 gm.)	1:80 ++−−	1:10 ++−−
Serum 92, the same as 91	1:40 ++++	1:10 −−−−
Serum 95, 4 injections of alcohol extract H597 (dry material injected 0.0093 gm.)	1.80 ++−−	1:320 ++++
Serum 96, the same as 95	1:10 ++++	1:20 ++−−
Serum 5, 3 injections of bacillary material thoroughly extracted with ether and alcohol (dry material injected 0.007 gm.)	1:40 ++++	1:20 ++++

extract cannot only vary according to the treatment of the animal, but with the same treatment one may meet with great variations. In the case of the tuberculous sera the affinity for the lipoid antigens, formerly

described, seems to be the rule. We have found the same thing to hold true in our diphtheria serum described in another paper. Whether this will be the general rule with every bacterium producing lipoid antibodies and with different other animals besides rabbits, we cannot decide.

The serum 95 gave us the opportunity to control the absorption experiments with the sera of only lipoid-treated animals. We could verify the circumstance that the treatment of the serum with the protein precipitate, made in the same way as formerly described, does not influence the antibodies of the serum. The same precipitate has absorbed all antibodies from the serum 81. The absorption with the alcohol extract has taken out the antibodies.

SUMMARY

According to our experience, the age of the culture and of the strain has no influence on the body's capacity to produce antibodies against the alcohol extract of tubercle bacilli. Injection of small amounts of culture arouse relatively smaller amounts of lipoid antibodies, as compared with the titre with the bacillary emulsion, than the injection of large amounts.

The mixture of proteins and alcohol extract is not more efficient in the animal experiment than either antigen alone. In the sera obtained after the injection of watery extract, even of very high titre, no lipoid antibodies are present.

There is described one rabbit serum, obtained by the injection of bacillary emulsion, nearly all the antibodies of which have affinities for the alcohol extract.

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SOME OBSERVATIONS ON THE CALCIUM-CHLORIDE TREATMENT OF TUBERCULOUS ENTERITIS[1, 2]

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Being considerably interested to note the effect of treatment with calcium chloride of patients suffering with enteritis of tuberculous origin, we began a search of the literature on this subject, and to make inquiry as to treatment along this line. The literature was very meagre except for a very good article by Ringer and Minor in the AMERICAN REVIEW OF TUBERCULOSIS, January, 1922. The information received by inquiry was of little value, because it was mostly hearsay and knowledge of only a few doses. Our institution being large, as to number of patients, here was an excellent field to give this treatment a thorough trial. This we have done for approximately two years, so that we have gathered the histories and conditions of a considerable group of patients who have completed several months of continuous treatment under our care.

Most of us know how difficult it is to keep a large number of patients under observation for a long time, but we have, on account of the large number of patients treated in our institution, been enabled to keep these for the period shown. These patients have had, as the others we are now treating, their injections once weekly, every five days, or twice a week. Those showing marked gastrointestinal symptoms are getting injections as often as twice weekly. The reason for the selection of treatment, as stated, is because of convenience of a weekly check, and because of a desire to keep them close enough together to prevent a relapse of the general effect. This is not an arbitrary interval and may be altered, for instance, as herein stated for patients suffering acutely from gastro-intestinal symptoms. There is a reason, I may state, for giving this latter group injections twice weekly; and that is, a temporary relief of symptoms lasting some three or four days. In order to keep this relief reasonably continuous, the twice-a-week schedule is adopted as long as we feel that it is needful. Then we drop back to the routine weekly

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[2] Published by permission of the Surgeon-General.

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schedule. There have been few treatments missed by any of these patients and they have all coöperated most sincerely and enthusiastically.

The standard dose of calcium chloride given has been a 5 per cent solution prepared in the following manner by our hospital laboratory: Crude calcium chloride is obtained and recrystallized. A solution of 5 per cent is then made in distilled water, and sterilized in the autoclave for one-half hour at fifteen pounds pressure. A small Erlenmeyer flask is used so that an opened flask will not be used again. The solution is neutral or slightly alkaline. Sterilization is done within twenty-four hours of use at our institution, but we do not know that this is altogether necessary.

It might be of interest at this point to give the technique of our method of injections. A 10 cc. syringe and number 18 needle are sterilized for each patient. The solution is warmed to body temperature, and poured into a sterile medicine glass to facilitate handling. The patient is then directed to place his arm across a table or high stool, palm up, and to grasp the upper arm with his free hand. This brings the veins out nicely. The arm is cleaned with iodine and alcohol (care should be used in the use of iodine, for repeated painting of iodine may cause severe burns). The syringe is filled to 5 cc. and the needle is inserted into the vein. A little blood is drawn into the syringe to make sure of proper location, and the injection is then given. The speed of injection is immaterial. We have tried it from two to three seconds up to two minutes without noting any difference in its effect. In connection with this technique, permit us to bring in a word of caution about injecting the solution outside of the vein. We have seen three cases in which this was done. And in one of these there was present for four or five days a marked and painful swelling of the entire arm from the wrist to the shoulder. This gradually subsided, so that in two or three weeks it was normal again. In the other two cases, ulcers about three-fourths inch in diameter formed, which gradually healed, at the time causing considerable local stiffness. These were more than two months in healing.

As to the diagnosis of tuberculous enteritis, we are confronted with the usual difficulties, and have been forced to resort to symptoms, X-ray findings, operative procedures for removal of appendix and subsequent autopsies. The making of a positive diagnosis of tuberculous enteritis in itself points out definitely that these patients have a very considerable amount of tuberculosis elsewhere, or such a spread of the disease would not be present. We do not know of any case of tuberculous

enteritis *per se*. Hence, we can readily see that the difficulty of permanent benefit to such individuals would be considerably increased. So the question then arises, what benefit can we expect from this or any treatment in a case that has definite involvement of the lungs and intestines, and almost certainly of other organs also. Needless to say, we cannot hope to effect an absolute cure of the intestinal condition, as long as there is continuous feeding from the involvement elsewhere by means of lymphatic or other extensions. But there appears to be benefit under this treatment, which we shall try to point out after giving the résumé of the physical condition, histories and laboratory findings. We shall not endeavor to give complete histories, but shall state cases as briefly as possible, consistent with giving all the necessary information. We have in our files, however, complete and exhaustive details of these cases, all of which have been gone over carefully.

GROUP 1

Case 1: Treated weekly for six months. Started treatment December 14, 1921, after about two years as infirmary patient, having been on the critical and seriously ill list on two or three occasions during that period.

At the time of starting treatment, diagnosis of tuberculosis, pulmonary, chronic, active, all lobes both lungs, with cavities both uppers. Pleuritic adhesions, left side. Laryngitis, chronic, tuberculous, ulcerated. Abscess of larynx, external, with drainage. Enteritis, chronic, tuberculous, ulcerated.

Progress notes show that the patient feels, eats and sleeps fairly well. Weight 106. Considerable cough and profuse sputum. Sputum positive. Maximum and minimum temperature, pulse and respiration, preceding treatment, 99.8°–97°, 106–78, 24–18. On special diet and tray, and a bed patient. Symptoms present at that time referable to gastrointestinal tract were severe abdominal pains daily, marked tenderness of abdomen, vomiting after meals daily, constipation, a fair appetite for a variety of food, but poor as to quality X-ray showed "Apparent spasticity through the colon, outline of the caecum irregular, a chronic cecal 'pathology' which is probably tuberculous ulceration."

At end of six months diagnosis was tuberculosis, pulmonary, chronic, active all lobes both lungs (slight) with cavity right upper. Pleuritic adhesions, bilateral. Laryngitis, chronic, tuberculous, nonulcerative. Enteritis, chronic, tuberculous, ulcerative.

Progress note shows that patient feels, eats and sleeps well. Weight 127 lbs. Cough and sputum slight. Sputum negative. Maximum and minimum temperature, pulse and respiration for one month, 98.4°–96°, 94–76, 28–18. Patient on general diet and eating at general mess. Symptoms referable to gastrointestinal tract are pains in abdomen about twice monthly, no tenderness, no vomiting, constipation, appetite good, both as to variety and quantity.

Gastrointestinal series taken at this time show "pyloric spasm present, no six-hour residue. The filling defect noted in the caecum on the former plates has almost entirely disappeared, and the outline of the large intestine is more nearly normal than on former plates. Considerable improvement is noted."

A comparative reading of chest X-ray plates taken at the beginning and end of treatment period shows, "There is an increase in the amount of fibrosis noted throughout both lungs, the amount of induration in the right lung, opposite the second and third rib interspaces, has decreased and the cavity in this area has thinner wall. Radiographic evidence of improvement noted in both lungs."

Treatment was discontinued after six months, and the patient has continued to show a gradual improvement, without recurrence of symptoms since that time, which has been more than a year.

Case 2: Treated ten months. Had pulmonary tuberculosis for a number of years and, to my personal knowledge, an infirmary patient for about two years preceding his beginning the treatment. Also has quite active bronchial asthma.

Condition at the start shows a diagnosis of tuberculosis, pulmonary, chronic, active, all lobes both lungs, with cavities both uppers. Pleuritic adhesions, bilateral. Bronchial asthma. Enteritis, tuberculous, ulcerative. (Patient was operated on for acute appendicitis a few months before calcium treatment was instituted and the tuberculous ulcers were seen by the operator.)

The progress note shows that the patient feels fair and appetite and digestion are fair. Weight 108. Cough and sputum considerable (200 cc. daily). Sputum positive. Has abdominal distress with distention. Maximum and minimum temperature, pulse and respiration for month, 98.6°–96.6°, 104–72, 24–20. Patient was on special diet and a tray case. Bed patient. Symptoms referable to abdomen were severe abdominal pain, daily vomiting after meals, considerable tenderness throughout abdomen, gas pains, constipation, very poor appetite, eating only soft diet.

At the end of twelve months diagnosis is unchanged.

The progress note shows that he feels, eats and sleeps well. Has considerable trouble with his asthma. Sputum and cough decreased about 50 per cent. Sputum positive. Weight 117. Maximum and minimum temperature, pulse and respiration, 99°–96°, 112–84, 28–20. Transferred to a convalescent ward and takes his meals at the general mess.

A gastrointestinal series taken four months after patient began treatment gave the impression as follows: "Probable caecal adhesions following appendicectomy."

A comparison of series of plates of the chest shows an increase in the fibrosis throughout both lungs. Pleuritic adhesions apparently increased.

Case 3: Treated ninety-one weeks. Had definite pulmonary tuberculosis since 1919 and in fair condition until about October, 1921, when he supposedly developed an "acute appendix" and was operated on. Marked intestinal ulcerations were found at this operation. Patient did not do well, and was apparently failing rapidly at time of his reëntrance to this hospital in December, 1921. His condition at that time was such as to place him on the seriously ill list.

At the beginning of his calcium chloride treatment, diagnosis was tuberculosis, pulmonary, chronic, active, all lobes right and left upper; inactive left lower, and with cavities both upper lobes. Enteritis, chronic, tuberculous, ulcerative.

Progress notes show that he feels, eats, and sleeps poorly. Weight 104. Cough and sputum slight. Maximum and minimum temperature, pulse and respiration, 101°–96°, 106, 26–18. Complains of severe pain in epigastrium and umbilical region, severe enough at times to require narcotic. Diet consisted of eggnogs only.

A gastrointestinal X-ray shows ulceration of caecum and terminal ileum, with reflex pyloric irritation. States that the ulcerations are probably tuberculous. (They were seen by operator two months before this.)

Symptoms referable to the gastrointestinal tract were very severe abdominal pains, marked tenderness around umbilicus and on right side, vomiting after meals or drinking anything other than eggnogs; constipation marked; no appetite.

At the end of a year's treatment the diagnosis was unchanged. Progress notes show that he feels, eats, and sleeps well. Weight 127. Maximum and minimum temperature, pulse and respiration, 98.6°–96°, 104–72, 24–20. Has occasional slight pain in abdomen; cough and expectoration slight. Sputum positive. In a convalescent ward and going to general mess. Appetite good. Symptoms referable to abdomen are slight occasional pain, some tenderness, no vomiting, bowels regular without the use of cathartics.

Comparison of the chest X-ray series shows that the mottling throughout the lungs has become more sharply defined, fibrosis has distinctly increased in the upper lobes and cavitation appears smaller.

Case 4: Treated six months. Had been under treatment about fourteen months before beginning calcium chloride treatment. Bed patient and semibed patient during this time.

Condition at starting of treatment shows a diagnosis of tuberculosis, pulmonary, chronic, active, all lobes right, inactive left upper. Pleuritic adhesions, right. Laryngitis, tuberculous, nonulcerative. Enteritis, chronic, tuberculous, ulcerative.

Progress notes show that he feels and sleeps fairly well; appetite and digestion poor. Weight 130, and losing weight rapidly, having lost 5 lbs. in past three weeks. Cough and sputum considerable. Sputum positive. Maximum and minimum temperature, pulse and respiration, 100.6°–96°, 98–82, 24–18. General abdominal tenderness, marked diarrhea, special diet, tray case, bed patient.

An X-ray of the gastrointestinal tract shows, "colitis, involving caecum, ascending and transverse colon, which is probably tuberculous."

Symptoms at this time referable to gastrointestinal tract are severe abdominal pains daily, marked abdominal tenderness, vomiting after meals, diarrhea, bowels moving six to eight times daily, appetite poor, being on a diet consisting of eggs, toast, and stewed fruits, of which he could eat very little.

At end of six months' treatment, diagnosis unchanged. Progress note shows appetite fair, feels fair and sleeps well. Weight 123. Cough and sputum decreased about 25 per cent. Sputum positive. Maximum and minimum temperature, pulse and respiration, 99.4°–97°, 104–72, 26–20. Special diet, tray case. Symptoms referable to abdomen, occasional slight pain, no vomiting, no tenderness, moderate diarrhea, bowels now moving two to three times daily, appetite fair, and eating a varied diet including the usual soft diet, with meat once daily.

Comparison of chest X-ray plates shows cavity in right upper to have decreased in size, parenchymal mottling more discrete than formerly, improvement being noted in right lung. No evidence of active lesions in left lung.

Case 5: Treated six months. A case of long standing pulmonary tuberculosis, having been discharged from Army in 1917 for it. Apparently active case since that time from history given. Had been in hospital a year at beginning of calcium treatment. Was transferred to an infirmary ward shortly before, because of retrogression.

At beginning of treatment, diagnosis was tuberculosis, pulmonary, chronic, active, all lobes both lungs, with cavitation both upper lobes and right lower. Pleuritic adhesions left base. Enteritis, tuberculous, ulcerative.

Progress notes show that he was sent to infirmary because of "increasing gravity of general condition," some thirty days before. Feels and sleeps fairly well. Appetite and digestion fair. Weight 148. Cough and sputum, slight. Sputum positive. Maximum and minimum

temperature, pulse and respiration, for the month, 99.2°–96°, 108–80, 24–20. Complains of indigestion and pains in the abdomen. Special diet, tray case, and bed patient.

X-ray of gastrointestinal tract shows "chronic ulcerative colitis, lack of normal haustrations from caecum to midportion of transverse colon, irregularity of outline and marked incompetence of the ileocaecal valve. Colitis is probably tuberculous in type."

Symptoms referable to gastrointestinal tract are some abdominal pain, which is not severe, slight tenderness, vomiting almost daily, diarrhea, bowels moving four to six times daily. Diet of milk, bread and eggs, not much in quantity.

At end of treatment (six months) diagnosis stood unchanged. Progress note shows that he feels, eats and sleeps well. Cough and sputum slight. Sputum positive. Maximum and minimum temperature, pulse and respiration for the month 99°–96°, 90–64, 24–20. Weight 148. General diet, and eating at the general mess. Symptoms referable to gastrointestinal tract are vomiting once in two or three weeks. There is no pain, no tenderness, the bowels are regular, twice daily, appetite good.

A comparative gastrointestinal series taken at this time shows, "Comparison with former plates shows some improvement in the ulcerative colitis, some normal haustrations being present in the colon. There is evident improvement in the condition of the intestinal tract since the last examination, the ileocaecal valve still being incompetent but not to the marked degree of the last examination. The same conclusions would be drawn, however, that of an ulcerative colitis, probably tuberculous."

Comparison of the chest plates shows walls of the cavities to be thinner with increase of size. There has also been an increase in the parenchymal mottling throughout. There is no evidence of improvement in the lungs and they are apparently slightly worse.

Case 6: Treated six months. Had been under treatment for more than a year, spending the first few months in an ambulant ward. Sent to infirmary with an acute extension seven months before calcium treatment started.

At beginning of treatment diagnosis was tuberculosis, pulmonary, chronic, active, all lobes right and left upper. Pleuritic adhesions both bases. Enteritis, chronic, tuberculous. Otitis media, chronic, suppurative. Syphilis, tertiary, latent.

Progress notes show that he feels, eats and sleeps fairly well. Weight 113½ lbs. Cough and expectoration moderate. Sputum positive. Maximum and minimum temperature, pulse and respiration, 102.2°–96°, 112–86, 28–20. Symptoms referable to abdomen were vomiting after meals, pain, losing appetite, considerable distention, and tenderness throughout abdomen. General retrogression. Special diet and tray case. Bed patient.

An intestinal X-ray was not taken because patient was considered too ill.

At the time of death, six months later, the diagnosis was unchanged except that pulmonary lesions had extended to all lobes.

Progress notes show that for the period of treatment the patient had had marked relief from his gastrointestinal symptoms in the face of definite retrogression elsewhere, the distention and tenderness having disappeared and vomiting occurring only at irregular intervals of three or four days. It was necessary in this case, however, to give the treatment twice weekly, for the reason that its effect would become negligible in about four days, and the symptoms above described would return.

Case 7: Treated five months. A young man of eighteen years, who had a fairly rapid course of his pulmonary tuberculosis, having been sick for less than a year at the time of his death. He was started on calcium chloride about seven months after he was first hospitalized.

The diagnosis at the beginning of treatment was tuberculosis, pulmonary, chronic, active, all lobes both lungs, with cavitation both uppers. Pleuritic adhesions both sides. Enteritis, chronic, tuberculous, ulcerative.

Progress notes at that time denote that he feels, eats and sleeps fairly well. Weight 118 lbs. Cough and sputum considerable. Sputum positive. Maximum and minimum temperature, pulse and respiration, 99.8°–96°, 118–84, 24–18. Symptoms referable to abdomen were vomiting after meals, poor appetite, tenderness, no diarrhea or constipation. Bed patient. Special diet. Tray case.

A gastrointestinal X-ray at this time gives filling defects in and around the caecum with tenderness in same region. Decrease in normal haustrations.

Diagnosis remained same at death.

After five months general condition had retrogressed to such an extent as to cause death. The above noted symptoms were markedly relieved until two weeks before his death, when they returned and were increased until the end.

A comparison of chest plates showed a continuous increase in the involvement of the lungs.

Case 8: Treated nine months. Had been under treatment for active pulmonary tuberculosis, peritonitis and enteritis for about three years. Had established a good resistance and was in fair condition, having always been an excellent patient to coöperate with his treatment as outlined.

At beginning of special treatment, diagnosis stood as tuberculosis, pulmonary, chronic, inactive both upper lobes, active right lower. Pleuritic adhesions right base (from old empyema). Peritonitis, tuberculous. Enteritis, chronic, tuberculous.

Progress note shows that the patient eats, sleeps and feels fairly well. Cough and expectoration slight. Sputum negative at this time. Weight 139 lbs. Maximum and minimum temperature, pulse and respiration, 98.8 –96.6 , 104–80, 24–18. Symptoms referable to abdomen show marked distention after meals with considerable pain accompanying. Moderate constipation. Patient up and about ward. Special diet.

A gastrointestinal series taken shortly before this time showed hypermotility of small intestine, with filling defects in caecum and loss of segmentation in ascending colon, which was regarded as suggestive of tuberculosis by the roentgenologist.

After nine months of treatment diagnosis remained the same, except that lower right lobe was considered inactive also.

Progress note gives information that he eats, feels and sleeps well. Cough and sputum very slight. Sputum negative. Weight 149 lbs. Maximum and minimum temperature, pulse and respiration well within normal limits. Abdominal symptoms indicate an occasional slight pain after meals, with no evidence of distention, and bowels are reported regular. General condition definitely improved.

A comparison of chest plates shows continued improvement, with an increasing fibrosis throughout.

Case 9: Treated five months. Had been under treatment for several years at different institutions, operated on for appendicitis, and with very little evidence of active tuberculosis in his chest at this time. Patient has had considerable heliotherapy treatment, which has improved his general condition.

At beginning of treatment, diagnosis was tuberculosis, pulmonary, chronic, inactive, both upper lobes. Pleuritic adhesions at right base. Enteritis, chronic, tuberculous. Abdominal adhesions, postoperative.

A gastrointestinal series was unnecessary, because the ulcerations were seen at the operation. Progress note gives record that he feels, eats and sleeps fairly well only. Cough and sputum are practically nil. Sputum negative. Maximum and minimum temperature, pulse and respiration, 99°–96.4°, 108–80, 24–18. Weight 150 lbs. Abdominal symptoms were marked diarrhea, eight to ten times daily, distention after meals with considerable pain. Special diet with ward privileges.

After five months of treatment, diagnosis remains the same.

Progress notes show that he feels, eats, and sleeps well. Maximum and minimum temperature, pulse and respiration remain unchanged. Weight 152 lbs. There is a marked improvement in the diarrhea, stools being well formed, and bowels moving four or five times daily instead of eight to ten times as previously noted. Gas pains are considerably decreased and appetite is improved.

A comparison of chest plates shows no changes of importance.

Case 10: Treated nine months. Had been under hospital treatment for two years and has been an infirmary case for past year.

Diagnosis at beginning of treatment was tuberculosis, pulmonary, chronic, active both lobes left and right upper, inactive right lower and middle. Pleuritic and pericardial adhesions, left. Laryngitis, chronic, tuberculous, nonulcerative. Enteritis, chronic, tuberculous.

Progress sheet gives evidence that the patient feels and sleeps fairly well. Eats poorly. Cough and sputum of moderate amount. Sputum positive. Maximum and minimum temperature, pulse and respiration, 100°–97°, 112–72, 24–18. Abdominal symptoms are pain after eating, with diarrhea lasting for a week to ten days, and then a four or five-day respite. Poor appetite. Special diet and not confined to bed. Weight 115 lbs.

An X-ray of the gastrointestinal tract gives the impression of general adhesions, a colitis with no normal haustrations present and with uneven filling defects in caecum, ascending, transverse and descending colon.

After nine months of treatment there is no change in diagnosis.

Progress notes show that patient eats, feels and sleeps well. Cough and sputum moderate. Sputum positive. Maximum and minimum temperature, pulse and respiration are within normal limits. Weight 119 lbs. There are no abdominal symptoms present for the past two months. A comparison of the X-ray plates of the chest shows slight increasing improvement.

GROUP 2

Case 1: Treated four months. Had been under treatment for pulmonary tuberculosis for about one year, and had been gradually retrogressing up to time of treatment. Diagnosis at the time, tuberculosis, pulmonary, chronic, active, all lobes both lungs, with cavities in both upper lobes. Pleuritic adhesions, bilateral. Enteritis, chronic, tuberculous.

Progress notes show that he eats, feels, and sleeps poorly to fairly well. Cough and sputum considerable. Sputum positive. Weight 115 lbs. Maximum and minimum temperature, pulse and respiration, 101.4°–97°, 122–80, 26–20. Abdominal symptoms are pain after eating, with some distention. A diarrhea of four to six times daily. Bed patient, tray case. Special diet.

A gastrointestinal series shows definite filling defects in the caecum and ascending colon.

After four months treatment, diagnosis was unchanged.

Progress notes show that patient died at the end of four months, that during this time there had been no evidence of any relief from gastrointestinal symptoms, and that during the last month of illness he had only two treatments of calcium chloride. Following both of these, there was a marked exacerbation of gastrointestinal symptoms. No further attempt was made to give treatment. Symptoms gradually increased up to death.

Case 2: Treated three months. Had been under treatment for pulmonary condition for about two years. Condition had been such as to require treatment on an infirmary ward but was not considered as retrogressing seriously until patient developed abdominal symptoms.

At the beginning of calcium chloride treatment, diagnosis was given as tuberculosis, pulmonary, chronic, active, all lobes both lungs, with cavities both uppers. Pleuritic adhesions, both bases. Enteritis, tuberculous, chronic.

Progress notes show that he feels, eats, and sleeps well. Weight 120 lbs. Cough and sputum slight. Sputum positive. Maximum and minimum temperature, pulse, and respiration, 99°–96°, 124–84, 22–18. Abdominal symptoms are pain after eating, and a moderate diarrhea, three to four times daily. Special diet. Semibed case.

A gastrointestinal series at this time gave indications of a hypermotility throughout the entire tract, with spasticity of the colon, most marked in transverse and descending colon.

At time of death, three months after treatment started, diagnosis was unchanged. Progress notes show that there was a constant increase of all abdominal symptoms above noted up to time of demise. The patient stated that after the first two or three doses there was absolutely no effect whatever. Diarrhea had increased to ten to twelve times daily.

GROUP 3

In Group 3, I should like to note merely that there were two patients who had active pulmonary tuberculosis, without any gastrointestinal symptoms, and who volunteered to act as controls and were consequently given treatment for a period of six months. A very careful check of these was kept as to all symptoms and pathological findings. There was no evidence of any change whatever in the condition of either of these patients, that we thought could be traced to the use of calcium chloride.

GROUP 4

Case 1: Treated one year. Had been under treatment for pulmonary tuberculosis, and for tuberculous fistula in appendix region, about three years before starting treatment, having been an infirmary case for the greater part of this time. This patient has also been under heliotherapy treatment for more than one year.

At beginning of treatment the diagnosis stands tuberculosis, pulmonary, chronic, active, in both upper lobes. Enteritis, chronic, tuberculous. (Ulcers could be seen through the fistula.) Fecal fistula, large, following appendicectomy in 1918. Peritoneal adhesions right iliac region. (These can also be seen.) Tuberculosis of genitourinary system.

Progress note at this time designates the condition to be stationary with a temperature, pulse and respiration range as follows: 98°–100°, 76–124; 18–24. The temperature rises daily. This is thought to be due to absorption from the fistula. Part of the intestine, seen through the fistula, is studded with small tubercles and some tuberculous ulcers. There are pains, and frequent micturition also. General condition is fair. Patient is confined to bed and is fed on tray.

The progress note shows that there is still present the same afternoon elevation of temperature, which existed before, which is accounted for by the absorption noted above and the new involvement. General condition is fair, with considerable symptomatic improvement. There is some excoriation of the skin around the fistula, which has shown marked healing, and the tubercles present one year ago have entirely disappeared. The patient received symptomatic relief from his calcium chloride treatment, but in this case it was possible to bring the sun's rays in direct contact with the ulcers and it is most probable that the healing present was due to this. (*Note:* Practically all of these tubercles had disappeared at the end of the fourth month of treatment.)

Comparative series of X-ray plates show some slight improvement present in the chest condition.

Case 2: Treated one year. Entered the hospital in 1918, because of abdominal wounds. A fistula formed, which was operated on several times, and finally healed in 1921. But in the meantime he had developed pulmonary tuberculosis, and so was forced to remain for

treatment. This gradually became worse until the patient died June 9, 1923. Patient had calcium chloride treatment for a little more than a year before his death.

At the beginning of treatment, diagnosis showed tuberculosis, pulmonary, chronic, active, both lobes left, and right upper. Cavity left upper. Pleurisy, chronic, fibrinous, left. Enteritis, chronic, tuberculous.

Progress note shows that appetite and digestion were good. Feels fairly well. Weight 152. Maximum and minimum temperature, pulse and respiration, 98.6°–96°, 120–80, 24–20. There was some abdominal pain present after eating, and vomiting at times. There is a record of increase in these pains in May, 1922, when the calcium chloride had been stopped about one month. He was started on treatment again in June, and symptoms above named showed considerable improvement.

A gastrointestional series showed that there were filling defects in the caecum, ascending and transverse colon, with lack of normal haustrations and evidence of considerable adhesions on the right side.

Diagnosis at the time of death shows activity present in all lobes, with the other diagnoses remaining the same.

Progress note shows that the abdominal symptoms began recurring about six months before death and gradually increased up to the end. The autopsy showed the presence of many healed ulcers, with some recent ulcerations which were active. (See discussion below.)

It will be noted that the above case reports were divided into four separate groups. The reason is obvious. Group 1 represents those which have shown relief or improvement of their gastrointestinal symptoms; group 2, those which showed negative results; group 3, those which were used as control cases only; and group 4, those which showed positive pathological healing. Checking the total number of case reports before us, we find them divided into the above four groups as follows:

	GROUP 1	GROUP 2	GROUP 3	GROUP 4
Cases	56	10	2	2
Per cent	80	14	3	3

I shall now discuss briefly these various groups in order to make our results as clear as possible.

In group 1, as may be seen, are some 80 per cent of the total cases listed. This percentage of relief of symptoms is rather better than we hoped for, because, as stated above, such cases are usually filled with tuberculous lesions elsewhere in the system. Nevertheless, the results quoted are present in these cases. It is not our desire to give the impression that these cases are all entirely relieved of symptoms, but it is our desire to impress the idea that the relief was sufficient to make life much more bearable and cheerful for these men. Only 20 per cent of the cases in this group showed apparent complete relief from their abdominal

symptoms. In addition to the relief of the gastrointestinal symptoms, a part of these cases showed a general improvement in their condition. Improvement was judged on these things: an increase in weight, decrease in cough and sputum, increase in fibrosis as shown by comparison of series of X-ray plates, approximation to normal of the temperature, pulse, and respiration; and evident improvement in clinical findings on examinations. Three of these cases, which also showed general improvement, have been followed up for more than a year after treatment was discontinued, with no evidence of recurrence of their abdominal symptoms, and with definite evidence of general improvement continuing. Before going on to the discussion of other groups, we should like to state that the relief from symptoms, *per se*, even if only partly due to calcium chloride, is sufficient to make this treatment worthy of serious consideration in every case of tuberculous enteritis, and in those cases with continuous abdominal symptoms, in which an absolutely positive diagnosis cannot be made; not, of course, in cases where symptoms are proved to be due to other causes than tuberculosis, such as chronic alcoholic gastritis, marked enteroptosis, etc.

In the second group of cases, ten in number, making up 14 per cent of the total reported, there was no evidence of improvement. There is a possibility that the symptoms were held stationary by this treatment, but it is evident that there can be no proof of this. One of these patients even stated that he had marked increase of symptoms for twenty-four hours after his injection. This case is reported above. Hence, we can only add that the results in this group were apparently nil.

As to group 3, as stated above, there was no change present during the treatment. One of these was active in all lobes, with cavitation in both uppers. He died later with spontaneous pneumothorax. There was no evidence of any gastrointestinal tuberculosis at autopsy. The other case was active in only one upper lobe, and has shown a gradual and continuous improvement for the past few months, since calcium chloride treatment was discontinued. There is nothing present to show that improvement is or is not due to calcium-chloride treatment in this person. It is understood that no conclusions can be drawn from two cases, but they lean slightly toward the idea of intestinal improvement.

In group 4 we have some very interesting results with regard to pathological findings. In the first case, there is the open fistula with lesions present which after a period have healed. The patient himself attributes this healing to his calcium-chloride treatment, but it is prob-

ably due to the combination of heliotherapy, gentian violet and calcium chloride, all of which this patient has had for the past year. The second case is of a man who died with extensive pulmonary tuberculosis. In spite of this fact, there is present a healed tuberculosis of the intestines. We realize that this is only one case, but are convinced that this opens up a most excellent field for further investigations. It also brings to our mind that there is a possibility of the pathological improvement being the cause of symptomatic relief in the above group of cases. This point is open to discussion.

In connection with this case, we present herewith a photograph showing the remarkable healing present in the ascending colon (fig. 1). In contrast to this is shown a picture of an intestine with advancing active ulcerations, and from a patient whose history showed no evidence of any gastrointestinal symptoms at any time (fig. 2).

There now come to us several questions on this subject, part of which can be answered and others which are more or less unsettled.

Does calcium-chloride treatment benefit a patient with tuberculous enteritis? We believe that the evidence is present of considerable symptomatic relief in a majority of patients treated. These patients received, of course, hygienic and dietetic treatment also, but in most instances this improvement was synchronous with the calcium-chloride treatment. But one might say of this symptomatic improvement, that, when the patient improves generally, his gastrointestinal symptoms will also improve. Our series shows that there was relief in all types of cases in face of the fact that the cases with both pulmonary and enteric tuberculosis rarely show any general improvement. Because of this we feel justified in giving credit to this treatment for relief of symptoms.

If so, then, how does calcium chloride reduce symptoms? It may be by an analgesic effect; it may be by the healing of ulcers; it may be by reducing the toxic secretions of the ulcers; it may be by combining with the toxins thrown off from the ulcerations or through some other chemical reaction; or it may be through the general property of calcium salts in relieving spasticity. These are some possibilities; but they are stated only as such and not as definite answers.

Now, if the calcium chloride improves the gastrointestinal symptoms, does it improve the chest condition? We do not believe that it does so directly. It probably does this indirectly by removing annoying symptoms which disturb the patient's rest and nutrition.

Another question arises at this point: Is the improvement only symptomatic, or is there some pathological improvement? Four of the cases reported here have been autopsied, with only one reported here showing healed ulcers. I should like to withhold any further discussion of this

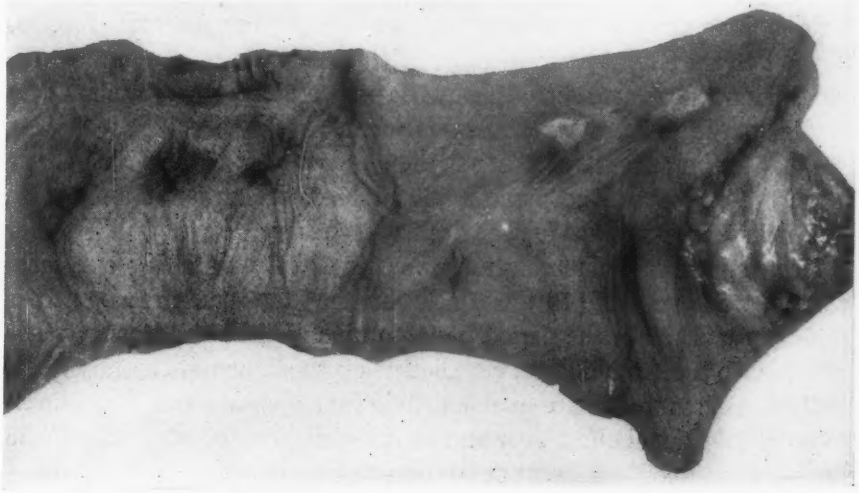


FIG. 1. CASE 2, GROUP 4, SHOWING HEALED ULCERS IN THE ASCENDING COLON

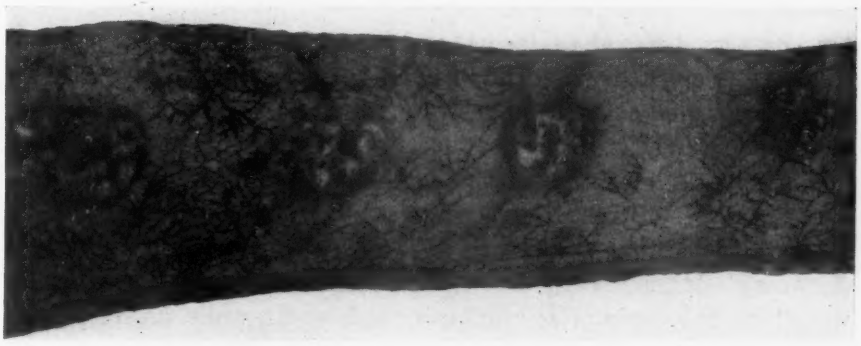


FIG. 2. CASE SHOWING MANY TUBERCULOUS ULCERS IN THE LOWER ILEUM AND CAECUM WITHOUT SYMPTOMS

The ulcers had caseous bases with marked inflammatory reaction

point at present, as it is our desire to give more information along this line at a future date.

What of cases who have tuberculous enteritis without any symptoms? We have given these cases calcium chloride treatment when known, but

have not been able to study the pathological results, as we have had no autopsies on any of them.

Do patients show relief from diet or heliotherapy? They do in many instances. In dietary relief, it is our experience that it is of a temporary character, and also that most patients will not follow dietary treatment for any great time. In heliotherapy, we believe there are some results, but not to the extent present under calcium-chloride treatment. However, dietary treatment should always be used, and heliotherapy should be applied to the abdomen whenever it is possible to do so.

What is the attitude of the patients, themselves, toward this treatment? They have all coöperated well, and have been more than anxious to continue treatment as long as deemed necessary.

How long should one continue treatment? By watching our cases closely, we have come to the conclusion that the maximum benefit is probably reached in the period between nine months and a year. The effect is, to a certain degree, cumulative up to six or nine months; but, in the few cases we have been able to hold for a year or more, there seems to be no additional effect over and above what is observed in those who have discontinued treatment at the one-year period.

The seventy cases on which this paper is based do not constitute the entire number of cases under treatment at this institution; but they do give a fair representation of the results as obtained here. These results have been good enough to lead us to adopt calcium chloride as a standard treatment, along with heliotherapy and dietetic treatment, for practically all cases showing evidence of gastrointestinal involvement. Again, we should like to advocate this treatment, both for the reason of symptomatic results and for the possible pathological improvement as well. Relief in either of these directions gives opportunity for the patient to increase his resisting powers for a fight against the infection in his body elsewhere. Inasmuch as a cure for tuberculosis has not yet been found, we believe this attempt at relief to be well worth while, as stated previously. Some of the cases which we considered practically beyond help have shown definite improvement in their condition, and consequently have at least had their lives prolonged very considerably.

In conclusion, permit us to say that we do not feel in any way that this treatment is a curative one, but we are presenting this paper only to bring to attention the good symptomatic results obtained with calcium chloride at this institution.

THE CORRELATION OF AUTOPSIES AND CLINICAL MEDICINE IN TUBERCULOSIS[1]

W. B. JAMESON

While Osler was Professor of Medicine at Johns Hopkins, he one night went from Baltimore to Carlisle, Pennsylvania, to obtain permission and made an autopsy on the body of a former patient. That was characteristic of the man. During the illness of the patient he studied function and the manifestations of disease and at autopsy he studied structural changes.

Surgery has substantially added to our knowledge of the anatomic features of disease and animal experimentation has immensely increased our comprehension of them, but it is autopsy that gives us the opportunity to study disease in its entirety, as it develops its destructive power in man.

The autopsy should not be a separate and detached entity; it should be part of the whole case and confirmatory or elucidative of the clinical study of the case. The clinical record, including the X-ray reports, should be present and reviewed at the autopsy. Autopsies of this character can add substantially to our clinical, laboratory and X-ray knowledge, and round out the complete picture of a disease. This is the reason for Osler's going from Baltimore to Carlisle.

Of the patients represented in this series of 100 autopsies made at the Hamburg (Pennsylvania) State Sanatorium for Tuberculosis, 10 had not shown clinical tuberculosis. One had clearly displayed an abdominal mass and had formerly been sent to a celebrated surgeon who refused to operate. Another surgeon, less celebrated and more audacious, opened the abdomen, saw the mass, pronounced it tuberculosis of the lymph nodes and closed the wound. It proved to be a carcinoma of the *caput coli*, with metastasis to the lymph nodes.

[1] A review ot one hundred autopsies performed at the State Sanatorium for Tuberculosis, Hamburg, Pennsylvania, with the approval of Dr. Henry A. Gorman, Medical Director, and Dr. Charles H. Miner, Commissioner of Health of Pennsylvania.

Another man who did not have clinical tuberculosis had worked many years in dusty shops. He was well nourished and had a good appetite and digestion, but he had moderate cough and marked dyspnoea. He was a healthy looking man but could not climb stairs or walk up a grade without discomfort.

At autopsy his body weighed 152 pounds and his heart 26 ounces. The left ventricle was hypertrophied and dilated. There was old, firm, fibrous thickening of the margins of the mitral leaflets, with contracture but not a button-hole opening. In addition to the mitral lesion there was a markedly granular, sclerotic kidney. Although the left ventricle was immense, the right ventricle formed almost the entire anterior surface of the heart. The right auricle, ventricle and tricuspid opening were enormously dilated and the right ventricular wall was about four times its normal thickness.

The right side of the heart was not able to send the blood through the lungs and a general congestion resulted. The long-standing congestion of the liver, spleen and kidneys produced in them cyanotic induration. The causes of the right-sided cardiac dilatation and hypertrophy were three,—emphysema, with the pneumonokoniosis that had produced it, and the left-sided cardiac lesion. The man's dyspnoea was due to his right cardiac lesion, his emphysema and his left cardiac lesion.

The remaining 8 cases which did not show clinical tuberculosis will not receive individual description. Since they were similar, only one of them will be described, that of a man who had been a coal miner for many years, always well nourished but becoming unfit for work on account of dyspnoea. Cough prevented his sleeping well and he was cyanotic.

Autopsy revealed old, moderately firm, fibrous pleurisy, marked emphysema and both lungs black from deposits of coal dust. The latter was most marked in the middle region, including the hilum, and next the upper part of the lung, and the least deposit of dust was in the lower lobe. The dust was laid down in masses more or less globular which varied in size from one-half inch to an inch and a half in diameter. The central part of the lung was almost solid.

Emphysema was marked. The heart had been so covered with lung that during life the apical impulse could not be seen and was only feebly felt. The left side of the heart was normal in size and not dilated. The right side of the heart was markedly dilated—auricle, ventricle and tricuspid opening—and the right ventricular wall was hypertrophied to three or four times its normal thickness, and was dark in color and firm.

Unable to pump the blood through the lungs, the right heart became dilated and hypertrophied and the blood produced general congestion. The liver, spleen and kidneys showed well marked cyanotic induration. The liver exhibited fatty infiltration and the kidneys moderate parenchymatous change.

The sequence of this man's pathological changes and symptoms was as follows: (1) The inhaled dust destroyed a portion of the vesicular tissue and the burden of respiration was thus thrown on the greatly reduced lung tissue that remained, thus producing compensatory emphysema. Indeed, there was practically no normal vesicular tissue left. In addition, there was a deposit of fibrous tissue that kept the dust in place. (2) All of these conditions interferred with the normal flow of the blood through the lungs and the excessive work placed on the right heart caused it to dilate and hypertrophy, the degree of dilatation being the index of its inability to do its work. The blood, which could no longer flow freely through the obstructed lung, congested the body and produced cyanotic induration of the liver, spleen and kidneys.

All of the patient's pathological changes, symptoms, distress and even death were therefore due to inhaled dust.

Of the 90 patients with clinical tuberculosis, 28 had pneumonokoniosis and emphysema, but all of the cases of lung tuberculosis had emphysema of the air vesicles immediately surrounding the tuberculous masses.

The right heart has its difficulty in advanced pulmonary tuberculosis. A portion of the lung is destroyed by cavitation, fibrosis or tuberculous masses, and emphysema weakens the usefulness of the remainder. Almost all of the hearts of our autopsy series showed atrophy, in common with the rest of the body. Generally, the surface was gelatinous and the blood vessels were tortuous; and there was always dilatation of the right auricle, ventricle and tricuspid opening and hypertrophy of the right ventricular wall. Again, with the inability of the right heart to perform its function, there was general congestion, with cyanotic induration of liver, spleen and kidneys.

Size of the heart: It has been taught that the heart of the tuberculous is small. The fact is often stated in the literature and only recently I saw the statement by a deservedly celebrated man. But while resident physician in the Philadelphia General Hospital and later assistant pathologist to the same institution, I was doubtful about the heart of the tuberculous being small in comparison with the size of the body. Only recently was it my good fortune to be able to weigh both the heart and the body.

Piersol's *Anatomy* gives the ratio of the normal weight of the heart to the normal weight of the male body as 1 to 169, and in the case of the female as 1 to 162. The ratio of heart weight to body weight in our more recent autopsies has been as follows:

For Males

No. 1	1 to 142
No. 2	1 to 165
No. 3	1 to 159
No. 4	1 to 147
No. 5	1 to 160
No. 6	1 to 159
No. 7	1 to 156
No. 8	1 to 148
No. 9	1 to 175
No. 10	1 to 174
No. 11	1 to 148
No. 12	1 to 140
No. 13	1 to 174
No. 14	1 to 154
No. 15	1 to 137
No. 16	1 to 148
No. 17	1 to 126
No. 18	1 to 165
No. 19	1 to 141
No. 20	1 to 182
No. 21	1 to 141
No. 22	1 to 148
No. 23	1 to 176
No. 24	1 to 135
Average	1 to 154

For Females

No. 1	1 to 193
No. 2	1 to 128
No. 3	1 to 157
No. 4	1 to 166
No. 5	1 to 140
Average	1 to 156

The cases of hypertrophy of the left ventricle due to sclerotic kidney and other causes were eliminated from the above series. The size of the heart in pure tuberculosis in this series is not reduced; indeed, it is somewhat larger than normal. The right heart always showed dilatation and hypertrophy.

Extent of pulmonary tuberculosis: Three bodies showed tuberculosis in one lobe, 5 in two lobes, 7 in three lobes, 2 in four lobes (the middle lobe of the right lung being free), and the remaining 73 in five lobes. Apparently, the disease in all cases started at the apex, and extended downward and into the other lung. Nearly all had some grade of cavitation.

One left lung had a cavity, the result of complete destruction of the tissues of the upper lobe, and a similar one in the lower lobe. In this case, as in all others, the pleura between cavities remained imperforate. Several others showed complete destruction of an upper lobe; but the common condition was that the cavities were multiple and not so large. Most of the cavities had irregular walls, without fibrous limiting membrane, but there were many that showed a more or less successful effort to limit the process, since they had smooth, fibrous walls and often the surrounding tissue was fibrosed. But very frequently a different picture was seen.

Even in the patients whose condition has been quiescent for a year or more there may develop an elevation of temperature and pulse, with loss of weight and eventual death. The common findings in such cases are

lungs fibrosed at one or both apices, with sharply limited cavitation, and nearly all the remaining lung tissue studded with tuberculous masses varying in size from an eighth to a half-inch in diameter. Frequently, even generally, the masses are about the same size, showing that they have a common origin. Occasionally tubercles are seen, but generally the masses are pneumonic.

Following a hemorrhage there is frequently a temporary rise of pulse and temperature, but when the rise persists and death ensues the necropsy is prone to show these widely distributed masses of tuberculous tissue. Generally the air vesicles between these masses contain an exudate. The extension, which occurred ordinarily a few months before death, involves usually all the lobes and nearly all the remaining vesicular lung tissue. It is surprising how small an amount of air-containing lung tissue can maintain life. The circumstance is due to the gradual development of the process and physical inactivity of the patient. Some chests showed only a portion of one lower lobe capable of respiratory function.

Sources of fatal hemorrhage: In four of the autopsies the ruptured blood vessel was found, three of which will be described. One man had had tuberculosis for ten or more years and for a long time had not shown activity. Moderate physical exertion could be maintained for a prolonged time without discomfort or any manifest ill effect. One night, about 1 A.M., while the nurse was making her ward-round, the patient, sound asleep, began to have a hemorrhage that gushed from his mouth and nose. Death came so quickly that it is probable that he did not fully realize what was happening. At the necropsy a large portion of an upper lobe contained only cavitation with well defined smooth fibrous walls surrounded by fibrous tissue. A cavity about two inches in diameter was opened by a small incision and the opening carefully extended to the walls of the cavity and a cross section made so as to obtain a good view of the interior. The blood was removed and a search made for the vessel. On the wall, near the floor of the cavity, was found a wide-open vessel about an eighth of an inch in diameter. More careful search showed a saucer-like fibrous cap attached to one side of the opening. The force of the circulation of the blood had been strong enough to sever the adhesion between the cap and wall, thus producing the fatal hemorrhage.

The second case also died quickly. The lung cavity was opened in the same way, but its outline was irregular and cords extended across it. One strand after another was investigated, until in one which had the

artery obliterated two-thirds of its length, and at the junction of the middle third with the patulous third, was found the opening. The wall of the aneurysm was apparent, but thin and badly lacerated.

The third patient had a small hemorrhage and died rather of suffocation than from loss of blood. The apparent cavities were opened by the same method and were found filled with blood, and the surrounding alveolar tissue contained an unusual amount of blood. The walls of the cavities were smooth and showed some fibrous tissue but no source of bleeding. The usual method had failed and a slash was made from apex to base. A small cavity of the same general character filled with blood and surrounded by bloody alveolar tissue was opened. The blood was removed, and a globular aneurysm, rather more than a quarter of an inch in diameter with laminated wall and ragged opening, was found.

The pleura: Every case of pulmonary tuberculosis showed chronic, fibrous adhesive pleurisy. In some of the cases the pleural cavity was obliterated in only the upper part, and usually the pleural thickening was greatest in the posterior upper region. Not infrequently the thickening in that region approached, and in some exceeded, a quarter of an inch. But, more frequently, the entire pleural cavity was obliterated by old, firm, slight or extensive adhesions. This is so common in tuberculosis of the lung as to suggest that it is a conservative process.

Pneumothorax: When this chronic adhesive process is absent or slight in part or all of the pleura, and an ulcerative process destroys the lung tissue so that the air from the bronchiole is in direct contact with the pleura, the unsupported pleura will almost certainly rupture and allow the air to escape into the pleural cavity, producing pneumothorax. In these 90 cases, pneumothorax was found in thirteen. All were partial; some were slight, while others were extensive; but not one caused direct collapse of the apex.

When the pneumothorax was large the lower lobe was extensively collapsed. This is due to the fact that the adhesions were less strong over that lobe. Frequently the lower lobe and the lower part of the upper lobe or the middle lobe were pushed up. In these cases the heart and mediastinal structures were pushed toward the other side. In the case of a small pneumothorax the adhesions may be so abundant that their contraction will draw the heart and mediastinal structures toward that side.

One small pneumothorax extended parallel with the costal margin from the anterior margin of the left pleura at the level of the nipple.

Its length was about five inches and its vertical dimension one and a half to two inches. The visceral pleura was but slightly thickened while the parietal pleura was a full quarter of an inch in thickness. The mediastinal structures and heart were drawn to the left.

One patient with a large cavity in the top of the left upper lobe developed a large pneumothorax which pushed both lobes well upward. The pleural cavity became filled with fluid and required tapping. Before the tapping the patient had severe pain over the front of the left side of the chest. A large amount of pus was removed at each tapping. At autopsy the pleural cavity was filled with pus, as was the cavity in the left upper lobe, and there was an acute plastic pericarditis. When the pus was removed two cord-like adhesions were seen. One extended downward from the lower part of the upper lobe and was attached to the pleuropericardial wall. This adhesion was about a half-inch in thickness and one and one-half inches long. The other adhesion extended from the lower anterior margin of the lower lobe almost to the lower limit of the pleuropericardial wall. It was four to five inches long and a quarter of an inch thick. The pain in the chest was doubtless due to the pull on the pleura and pericardium from the upward pressure on the lung. The respiratory function of this lung was entirely suspended.

There was one hemopneumothorax. It contained about a quart of soft, jelly-like clots and bloody fluid and a pint of air. The remainder of the pleura was obliterated by an old, firm, thick layer of fibrous tissue, part of which was fully a quarter of an inch thick.

One case of pneumothorax communicated with a lung cavity, and so much of the cavity wall had been destroyed that the opening was very large and the line of separation between the lung cavity and the pneumothorax was not apparent on superficial inspection. Naturally, it had all been diagnosed as a lung cavity.

The duration of life after the development of pneumothorax in these cases cannot be estimated because the condition in some of them was not recognized before autopsy. But none of the patients died soon after the development of the pneumothorax.

There was not a case of hydrothorax, but one case of serothorax, four of empyema and one of hemothorax. In the last case 700 cc. of bloody fluid had been removed from the left chest eight months before death. At autopsy there was a small left pleural space containing a few ounces of clear fluid. The visceral layer of the pleura was about an eighth of an inch in thickness, while the parietal layer was from a quarter to a

half-inch, and the thickest part was toward the costal margin. The right pleural cavity contained about a pint of bloody fluid, in which were trabeculae extending from one pleural layer to the other, showing a low grade of organization. The pleura showed thickening similar to that found on the left side, but it was soft and poorly organized. Both upper lobes had a moderate number of recent tuberculous masses about an eighth of an inch in diameter, but there were none in the other lobes. The lower portion of the right lobe was compressed and heavy but not wholly devoid of air. The peritoneum covering the right diaphragm was studded with tuberculous masses about an eighth of an inch in diameter and a similar condition involved the peritoneum down to the kidney.

Abdominal lesions: The state of the digestive and assimilative function is an important factor in the prognosis of tuberculosis. We are quite prone to attribute all the abdominal discomfort and poor function of the disease to the pulmonary lesion. Surely, there is justification for the view that the pulmonary condition is responsible for the development of nearly all, if not all, of the tuberculosis of the alimentary tract in adults. By far the most serious lesion of this character in these organs is found in the intestines.

At 35 of the autopsies typical tuberculous ulcers were seen in the small intestines, and 32 showed characteristic ulcers in the colon; and in all the cases there was tuberculosis of the appendix. Six cases had ulcers in the small intestine and none in the colon, while 3 had ulcers in the colon and none in the ileum.

In the small intestines, unopened, the ulcers can be located by the congestions and the appearance of tubercles under the peritoneum. Occasionally, there is a little plastic exudate over the ulcer on the peritoneal surface. When viewed from the mucous surface the ulcers are transverse and deep with overhanging edges. The ulcers are so deep that it is remarkable that perforation is so rare. However, in one of these cases two folds of ileum were firmly adherent over an area of almost an inch in diameter. On opening the folds an ulcer in each one was found under the area of adhesion. The union of the two folds was firm.

In the colon the location of the ulcers was not indicated by tubercles under the peritoneum, but the tube was injected and thickened. The *caput coli* and ascending colon showed the greatest involvement. The ulcers were deep, and generally spindle-shaped with overhanging edges.

They were not so numerous in the transverse colon and frequently they approached the quadrate form. Occasionally ulcers of this general form were found in the descending colon.

In the cases of tuberculous colitis with diarrhea the portion of the tube having the ulcers contained little or no fecal matter, while those that did not have diarrhea showed an abundance of fecal matter in the region of the ulcers; but there was nothing to explain why some had diarrhrea and the others had not.

One patient had had tuberculosis of both upper lobes with cavitation long enough to develop a 12-ounce amyloid spleen. For three years his pulmonary process had been reasonably quiescent; he had been able to do a moderate amount of work without failure in condition. But he had trouble with his stomach. Eventually he lost endurance, strength and weight, and developed diarrhea with pain in the abdomen and nausea with frequent vomiting with gastric pain and a burning pain along the line of the oesophagus. His pulse and temperature were moderately increased, but not in keeping with the gravity of his condition.

At autopsy the old pulmonary lesions with cavitation and fibrosis were found, but there was no recent tuberculous extension. The intestines showed ulceration above and below the ileocecal valve. There were no ulcers in the stomach, but there were many erosions in the oesophagus that were not tuberculous ulcers. There was an extensive old fibrous adhesion between the deep part of the gall bladder and the pylorus, and the pylorus was drawn up close to the gall bladder. The duodenum left the pylorus at a sharp angle. It seems reasonable to believe that the adhesion between the gall bladder and pylorus was responsible for the gastric pain, vomiting and erosion of the mucous membrane of the oesophagus through the irritation of gastric secretion.

This was the most marked pathological adhesion of the gall bladder in these hundred autopsies, but there were 57 other gall bladders which showed abnormal adhesions to adjacent structures.

Gall stones: Four gall bladders contained gall stones. One had one large stone and several minute ones, all globular. The others were also spherical. One contained three stones in three freely communicating compartments of the bladder.

An elderly man, nearly blind from cataracts, extremely deaf and suspicious as many deaf people are, a coal miner of many years, had a troublesome cough, dyspnoea, a bad temper and complained of indefinite upper abdominal distress. At autopsy the usual pneumono-

koniosis and emphysema were found associated with the dilated right heart and hypertrophy of the right ventricular wall, with cyanotic induration of the liver, spleen and kidneys. In addition the man had two spherical gall stones floating freely in an enlarged gall bladder. The gall bladder showed well marked old firm adhesions to the transverse colon and its mesentery. There was no gross lesion of the stomach, but the beginning of the duodenum showed a deep, inactive ulcer, oval in shape, one inch by three-quarters of an inch. The diagnosis had not been made. But with a man so deaf, so suspicious and bad-tempered I have no apology to offer for my associates and myself.

Appendix: When there are digestive disturbances the appendix deserves investigation. In this series of a hundred cases, one appendix had been removed, two were the seat of acute appendicitis with perforation in a tuberculous organ, and eighty-two others showed tuberculosis or chronic fibrous adhesions. Most frequently the adherent appendix was directed downward into the pelvis and next frequently they extended upward.

The location of one was unusual. It lay close to the deep part of the gall bladder and was bound to it and the adjacent liver on the right. The first portion of the colon had a mesentery long enough to allow a fold to extend down almost to the pelvis. There doubtless had been at least one attack of appendicitis and the question arises as to what diagnosis was made.

Amyloid disease: Barker states that amyloid is far less common than formerly because of the earlier recognition and the better treatment now of chronic suppurative processes, tuberculosis and syphilis. In general, the statement is doubtless true, but since the patients with tuberculosis live longer the prospect is not good for a marked reduction in the percentage of amyloid in the tuberculous. In this series of autopsies 19 showed amyloid of the spleen, 11 of the liver, 4 of the kidney and one of the suprarenals. In one there was amyloid of the liver alone and one of the liver and kidney. In the spleen, amyloid is the most common and the most marked.

One of these patients during life had an enlarged, painless liver, enlarged spleen, an abundance of clear, amber urine of low specific gravity and containing a moderately marked amount of albumen and slight sediment with many casts, and a heart not especially enlarged. According to Leube's rules amyloid kidney should exist and the case was used in clinic to show a case of amyloid of the spleen, liver and

kidney. But at autopsy the liver and spleen ran true to diagnosis, while the kidney showed cyanotic induration and parenchymatous nephritis. The writer has always been cautious about making a diagnosis of amyloid kidney and the above experience strengthens his attitude.

An enlarged painless liver is due to fatty infiltration or amyloid, and not one of these cases showed an enlarged fatty infiltrated liver. On account of the former method of stuffing tuberculosis patients with fatty foods the large fatty infiltrated liver was common. An enlarged fatty infiltration of the liver is to-day so rare that an enlarged painless liver in tuberculous patients should be called amyloid.

In only one case was amyloid found in the suprarenals. Those organs were enlarged with rounded edges, and were firm and elastic and with Lugol's solution showed marked amyloid.

The intestines were stained for amyloid but without success.

Lymph nodes: In all cases of tuberculosis of the intestinal tract the corresponding lymph nodes were enlarged, but rarely were they larger than a kidney bean and they were not soft. In one case the nodes were almost an inch in diameter and soft. These were above the pelvis to the right of the spinal column.

The peribronchial and mediastinal nodes were always enlarged and pigmented but almost never softened. In some of the anthracosis cases, the lymph nodes were an inch to an inch and a half long, black and even gritty.

One case of anthracosis had especially large black lymph nodes in the mediastinum and the nodes below the diaphragm were somewhat enlarged and pigmented as low as the solar plexus. The nodes below that point were normal in size and color.

Attention has already been called to the fact that in all cases of dilatation of the right heart with hypertrophy of the right ventricle there was cyanotic induration of the liver, spleen and kidneys. In addition five livers were of the moderate hobnail class. Nine necropsies showed granular kidneys, and the kidneys of all who had died of tuberculosis of the lungs, pleura or intestines showed more or less extensive parenchymatous nephritis.

Two autopsies showed tuberculosis of the spleen, nine of the kidney and no gross tuberculous lesion of the liver or suprarenals.

In but one case of meningitis were we permitted to examine the brain. It showed the usual exudate of pus and fibrin with early tubercles of the vessels on the perforated spaces.

CONCLUSIONS

1. All autopsies should be a part of the clinical study of the cases.
2. Tuberculosis produces an enormous range of pathological changes.
3. Any lesion of the lung which interferes with the flow of blood through the vesicular walls causes overloading of the heart, dilatation of the right auricle, ventricle and tricuspid opening and hypertrophy of the right ventricular wall, and general congestion with cyanotic induration of the liver, spleen and kidneys.
4. Amyloid disease quite frequently adds its influence to the destructive power of its progenitor, tuberculosis.
5. Diseases of the appendix and gall bladder are so common and their disturbance of the digestion so frequent that they constitute a serious handicap to a person with tuberculosis.
6. The toxic influence of tuberculosis before death develops parenchymatous nephritis.

IMPRESSIONS OF TUBERCULOSIS WORK ABROAD

RANDALL CLIFFORD
Boston

The thoughts of the medical profession of this country were moulded during the nineteenth century by three schools. In the early part of the century American students went principally to Edinburgh and to London; then followed a period when the teachings of the French school dominated, and Paris formed the chief centre of medical education. German influence next prevailed, until in the early part of the twentieth century America took a leading part in medical progress and education, and foreign students began to come and are still coming more and more to this country for their instruction and postgraduate work.

Although we hold this leading position today, we must not, however, lose sight of the valuable work which is being done in other countries. The fact that such a danger exists was brought to my attention by a remark made to me just before my departure for Europe: "You will have a wonderful time, but I doubt if you will learn anything new." If we wish to keep our place in the medical world, we must not only combine, with our own scientific advance, the results of foreign achievement, but we must also keep in close touch with the methods used by other nations in dealing with the same problems with which we ourselves are confronted.

In the short time at my disposal, it was my object not to go into any detailed study, but rather to gain a general impression of the foreign methods of treating tuberculosis, as one of the most important diseases of the chest.

Paris offers an excellent opportunity for studying the French methods of dealing with this disease, and for meeting the men who are most active in this work. It was intensely stimulating to talk with such men as Doctors Sergent, Bernard, Bezançon, Rist and Kuss, and to follow their clinics. The keenness of their observation, their characteristic enthusiasm, the depth of knowledge and breadth of experience, revealed in the detailed discussions of their clinical cases, were very striking. The influence of these men is being felt not only in their hospital clinics but

also in the nation-wide movement toward organization of the forces combating tuberculosis.

The *Comité National de Défense contre la Tuberculose* is striving to organize all the work, private, public, institutional and legislative, for the purpose of coördinating and directing local efforts. In this the Rockefeller Commission has been of great assistance. A very important part of the work deals with the problem of prevention. The *Placement Familial*, started by the *Société Grancher*, takes healthy children away from infected parents and places them with healthy families in suitable homes in the country. Preventoria are scattered in large numbers throughout France, notably in Brittany and on the outskirts of the larger cities. The Preventorium of Plessis-Robinson near Paris accommodates over two hundred children of both sexes and, with its many acres of woodland, is an excellent example of what can be done near a large city. The Preventorium of the Forest of Neuhof, within four kilometres of Strasbourg, with delightful open-air pavilions for rest, play and study, is another excellent illustration of this type of work.

Another very important feature of the tuberculosis organization in France is the hospital isolation service. Special quarters are being set aside in some of the larger hospitals of Paris, such as the Laennec, Boucicaut, Hôtel-Dieu and others, for those cases that must be under observation before a final diagnosis can be reached, for those that cannot be treated at home on account of the acuteness of the attack, and for those in the last stages of the disease. It seems to me that this feature might be made a part of our hospital organization and would be of great value not only in caring for the tuberculous, but also in facilitating the study of the disease.

As a part of the educational work that is being done by the *Comité National*, conferences are being organized in various cities throughout France. The national conference was held this year at Strasbourg and was of especial interest owing to the celebration of the Pasteur Centennial, drawing representatives from many countries. The subjects discussed dealt with the educational and scientific aspects of the tuberculosis problem in France to-day. Particular stress was laid upon prevention. Among other features which made this conference of peculiar interest, were the visit to the splendidly equipped hospital which was remodelled shortly before the war by the Germans, who had installed most complete modern equipment, and the Pasteur Centenary international exposition of laboratory equipment used by Pasteur, photographs and models in wax of all the branches of his works.

During the conference a visit was paid to the sanatoria of Aubure and Salem, beautifully situated in the Vosges Mountains. In France, the *Sanatoria de Cure*, which are usually situated at a high altitude in the country, are distinctly separate from the Hospital-Sanatoria which are within reach of the cities. The former take only those cases in which there is a possiblity of cure, and it is to these that each Department is obliged to send its curable cases under the *Honnorat* Law of 1919; the latter take serious and fatal cases in addition to those which are curable. At Hauteville the Sanatorium Mangini, in charge of Dr. Dumarest, and the Sanatorium d'Angeville, under the direction of Dr. Louis Rochette, were both of great interest. The type of work that is being done at these sanatoria is most excellent; an important feature of their treatment is artificial pneumothorax.

After leaving France, it was most interesting to visit the clinic of Dr. Cevey at Sylvana-sur-Lausanne, Switzerland, a private sanatorium in a charming location with a view across Lake Geneva to the Alps. In discussing the effects of altitude upon tuberculosis, Dr. Cevey expressed the frequently advanced opinion that in many cases patients who have undergone treatment for a long time at a very high altitude suffer a relapse upon returning to a lower level and are therefore forced to remain for years at the higher altitude, an opportunity within the reach of comparatively few persons. He felt that tuberculosis could be treated successfully in any climate and at any altitude and that, until we have a specific cure, we must supplement nature's effort to increase individual resistance by combining all our known recognized methods of treatment, not relying upon one method alone at the expense of the others. He made a very interesting investigation in the treatment of fifty undernourished children from the devastated regions, all coming from infected and overpopulated lodgings and all infected with tuberculosis. He is convinced that in a large number of such cases it is the underlying tuberculous infection which causes the debilitated state of the child, and that it is not the undernourishment that is responsible for the disease. He is further convinced that in those cases "predisposed" to tuberculosis it is not sufficient simply to give them good food, rest and fresh air, but that furthermore the disease itself should be treated by the intelligent use of tuberculin in doses sufficiently strong and frequent to produce immunity before the disease has too firm a hold. Another important point which he emphasized was the prevalence of tuberculous infection among children of school age. In a very interesting

study of a normal Swiss village he found that between the ages of seven and ten 29 per cent of the children were infected with tuberculosis, between the ages of ten and fifteen 61 per cent were infected and many more children who were attending school were infected than those of the same age who were not in school. These observations bring up many interesting and vital questions.

At Leysin, Switzerland, there are numerous sanatoria for pulmonary tuberculosis. Few places are more widely known than the clinic of Dr. Rollier, mention of which should not be omitted, although it is for the treatment of surgical tuberculosis alone. Situated more than four thousand feet high on the sheltered side of a mountain, Leysin is peculiarly adapted to heliotherapy, as the air is very clear and dry and there is very little wind, factors which are of great importance in this form of treatment. Dr. Rollier believes in the small unit system; consequently one sees many small cottages scattered over the mountainside. Every patient is thoroughly studied and acclimatized to the high altitude before beginning the gradual and graduated exposure to the sun. In seeing so many patients in all stages of this disease, one is impressed with the cheerfulness and happiness of all, particularly the children, many of whom, bedridden for months, are smiling and happy; and one cannot fail to realize not only the hygienic value but also the moral effect of sunlight in the treatment of disease.

In contrast to the high altitude which is so characteristic of the treatment of tuberculosis in Switzerland, it was of great interest to visit Edinburgh, Scotland, and to have the opportunity of seeing the work that is being done by Sir Robert W. Philip. Professor Philip was the first to organize systematically an antituberculosis campaign and, in Edinburgh in 1887, founded the first tuberculosis dispensary. With breadth of vision and foresight he has emphasized the fact that in order to be successful in our fight against this disease there must be complete coördination of all parts of the organization, and that no one branch should be undervalued any more than any one accepted method of treatment should be neglected. His Edinburgh system has been copied in many respects in this country as well as in other countries. In this system the dispensary forms the centre. Here cases are sifted out and sent either to a sanatorium or to a hospital for advanced cases. Doctor Philip feels that the examination of the contact cases is of the utmost importance and that, when a case of tuberculosis is discovered at the dispensary, all other members of the patient's family should be sub-

mitted to a thorough examination. In this way advice and treatment can be given, early cases discovered and nests of tuberculosis exposed. The Royal Victoria Hospital takes almost exclusively acute cases; but, in addition to the regular patients who stay from three to four months, there are also the so called visiting patients who go to the hospital each day and receive instruction and treatment, returning at night to their homes. Another feature of the treatment in this hospital is that all patients, when able, are assigned some form of graduated exercise. The hospital for advanced cases forms another necessary link in the chain and needs no explanation.

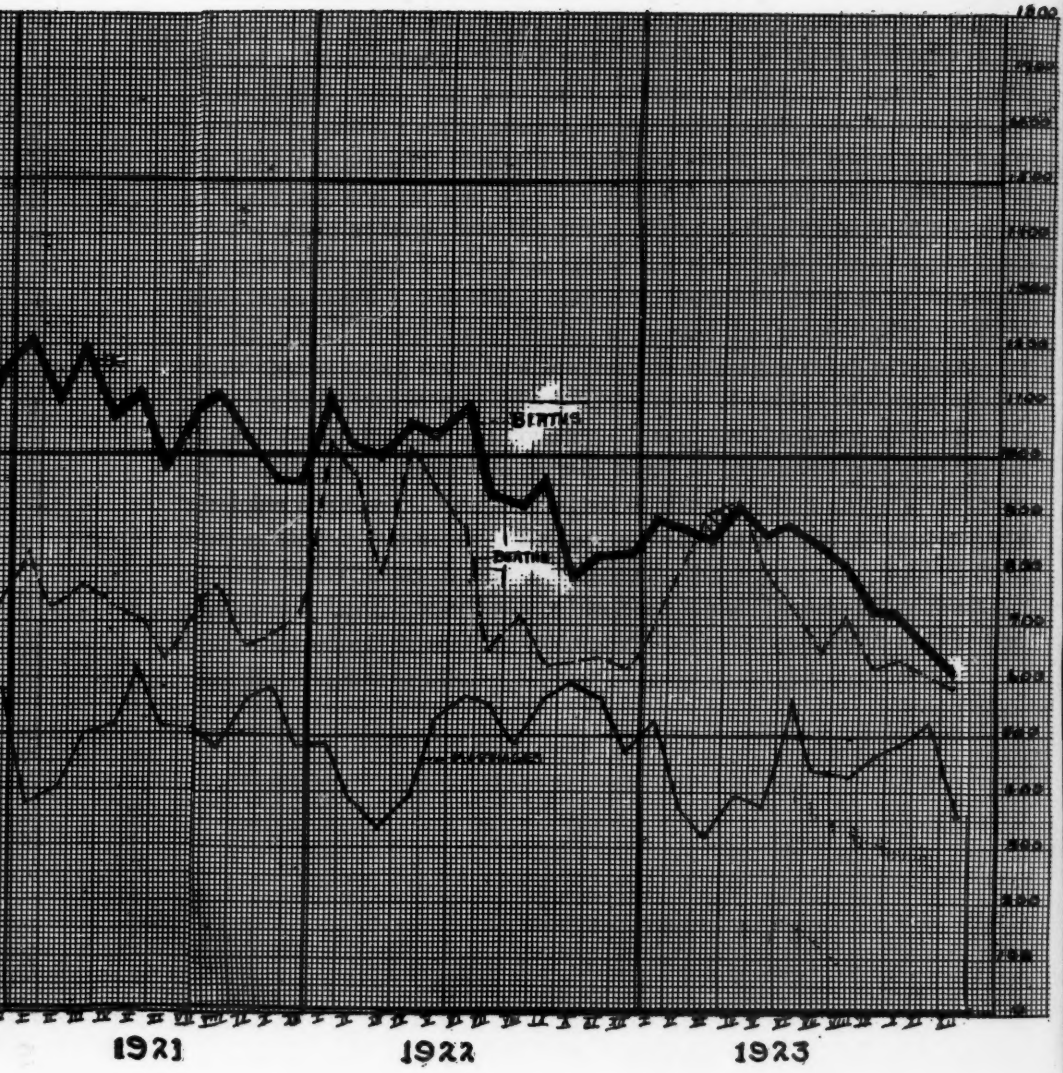
A very important phase of the work is being carried out at the Farm Colony. Many patients from the Royal Victoria Hospital are sent there before returning to their homes and are given different forms of work, such as gardening, care of live stock and tasks of a similar light nature. Doctor Philip has gathered at this colony, where they are under the constant supervision of Doctor Simpson, cases of all types, pulmonary and nonpulmonary, in order that the disease may be studied as a whole. At the time of my visit, a new laboratory for research work was in the process of construction. This entire unit offers an unusual opportunity for combining clinical study, research and treatment. Doctor Philip's view in looking at tuberculosis in its broader aspects is most stimulating. He emphasizes the value of early diagnosis and lays great stress on systemic intoxication, believing that, although one organ only may be infected, we must not lose sight of the possibility of the toxic manifestations and the slow advance of the disease through the whole system. We must therefore learn to diagnose and institute treatment in the seedling stage of the disease and not wait until it has blossomed into full flower.

To attend the National Tuberculosis Conference at Birmingham, England, was to obtain a comprehensive view of many interesting aspects of the tuberculosis problem in Great Britain. Among the subjects discussed were the infectivity and segregation of the advanced case of tuberculosis, the problem of infected milk, the prevalence of tuberculosis among workers in different trades, the value of notification, and the importance of educating the public in the necessary methods of prevention. The conference closed with a most excellent address by Sir Robert Philip, outlining his views on the outlook of the tuberculosis situation to-day, based on his experience of the last forty years.

After the brief glimpse afforded by the Birmingham conference of some of the work being done in England, it was most interesting to visit some of the London hospitals. At the Brompton Hospital for Diseases of the Chest, many interesting types of work were being carried on. A great deal of artificial pneumothorax work is being done there, not only in the tuberculosis cases, but also in a certain number of nontuberculous pulmonary cases, such as abscess, bronchiectasis and recurrent hemoptysis, with encouraging results in many instances. An important feature of the work, and the one which is, perhaps, being watched most closely by the world at large, was the group of cases of pulmonary tuberculosis being treated with Dreyer's antigen. However, until many more cases have been treated with this, no opinion should be given as to its value.

The field of tuberculosis, to-day, is so vast that a brief glimpse of the work that is being done in a few foreign countries must necessarily be very limited in its scope. Much of the work abroad is, of course, similar to that being done in this country. There are, however, differences in the importance attached to certain forms of treatment and even in the methods employed. We may agree or disagree with any one of these; but, as Doctor Philip says, the key to complete success in the campaign against tuberculosis is the harmonious coördination of well-directed measures. Until a specific cure has been found, therefore, we must not lessen our efforts in seeking to combine with our own methods the best that Europe has to offer.

1918
1919
1920


1921
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1923

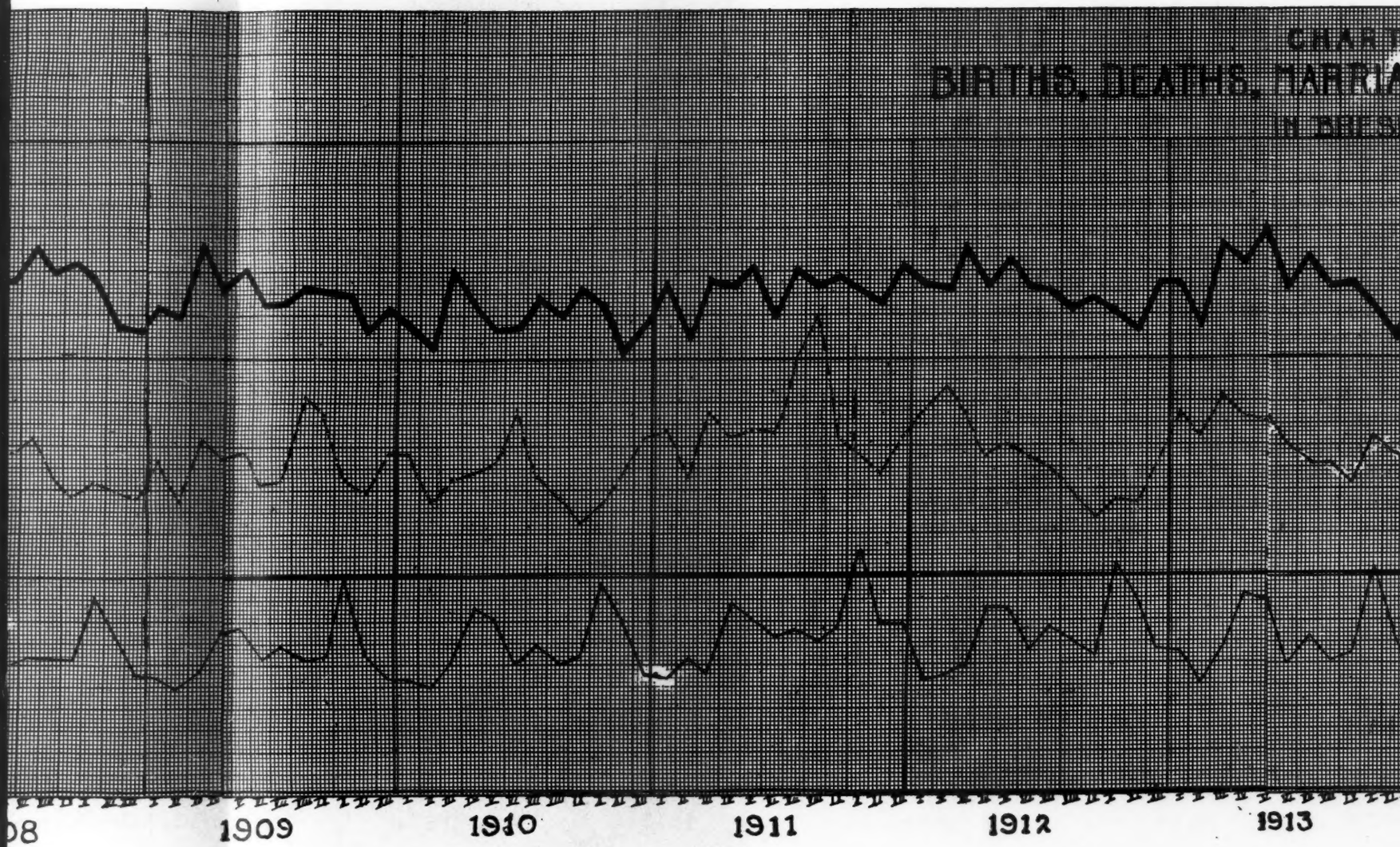
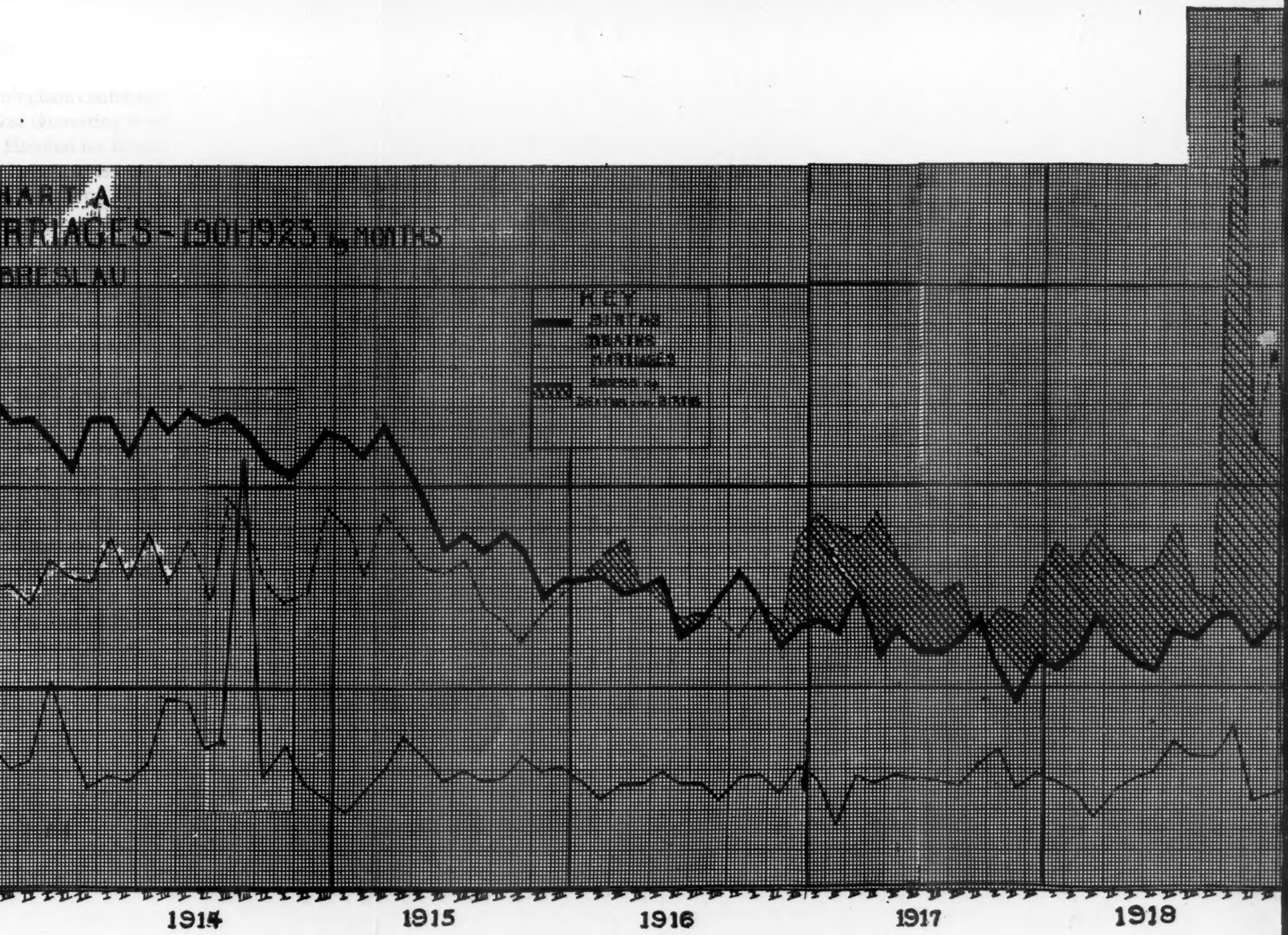


CHART A

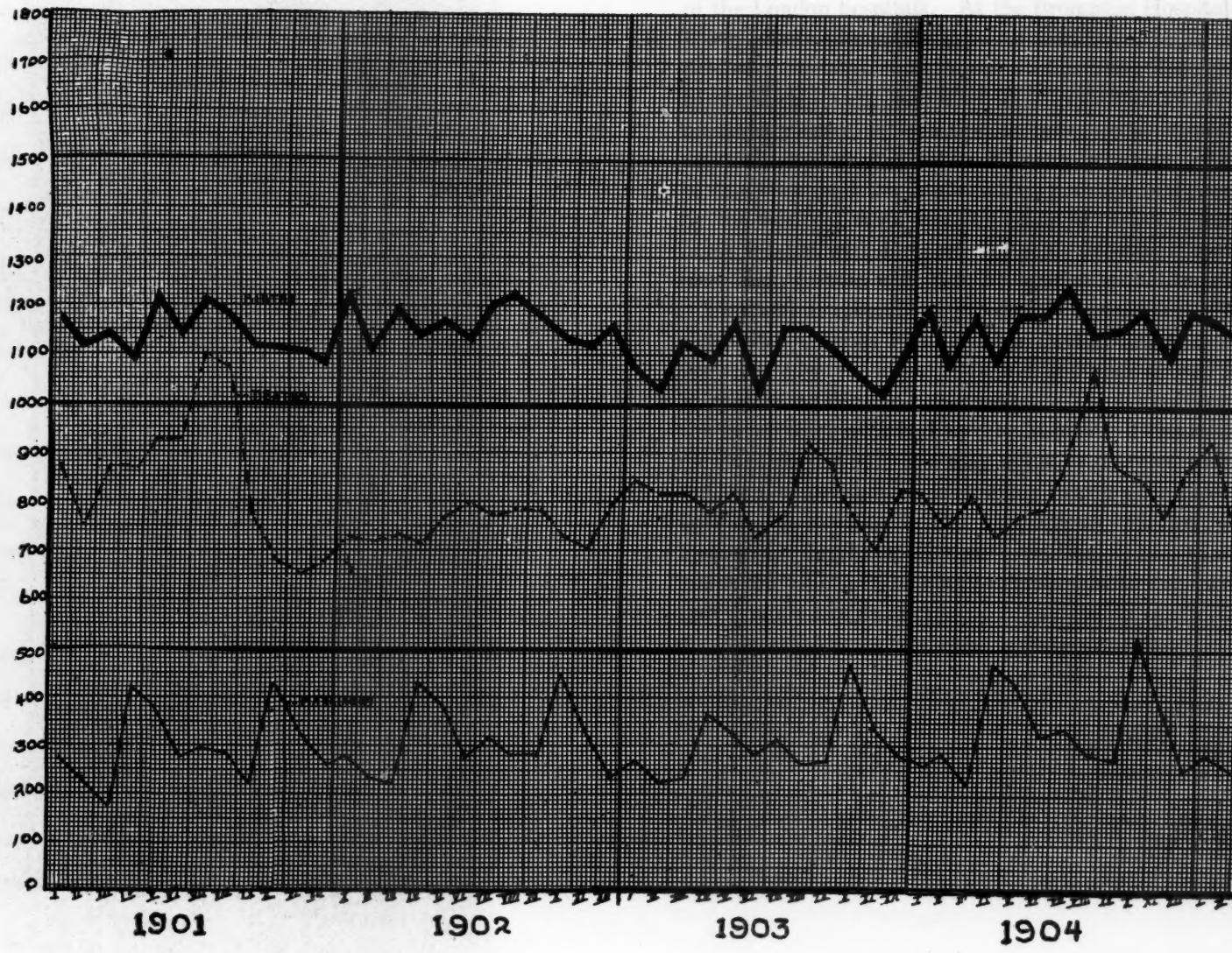
The population of Germany has been affected generally in all cities and almost to the same degree in the rural areas, by the changes in deaths, for the city of Breslau.

The effect of the mobilization of August, 1914, upon marriages, the continued reduction of births until they were exceeded by deaths in the after until August, 1919, the great excess of deaths resulting from the influenza epidemic of September and October, 1918, and the subsequent the spring of 1919 and in the winter of 1920, the gradual increase in marriages during the year following November, 1918, the tremendous increa births since June, 1922, to a level in November, 1923, about half the monthly prewar births, all appear in the sequence of events in an accurate



s in deaths, births and marriages, as recorded in chart A

eaths in the winter of 1916 and pretty regularly there-
subsequent three recurrent waves in December, 1918,
ndous increase in births, and finally the reduction in
an accurate and graphic record.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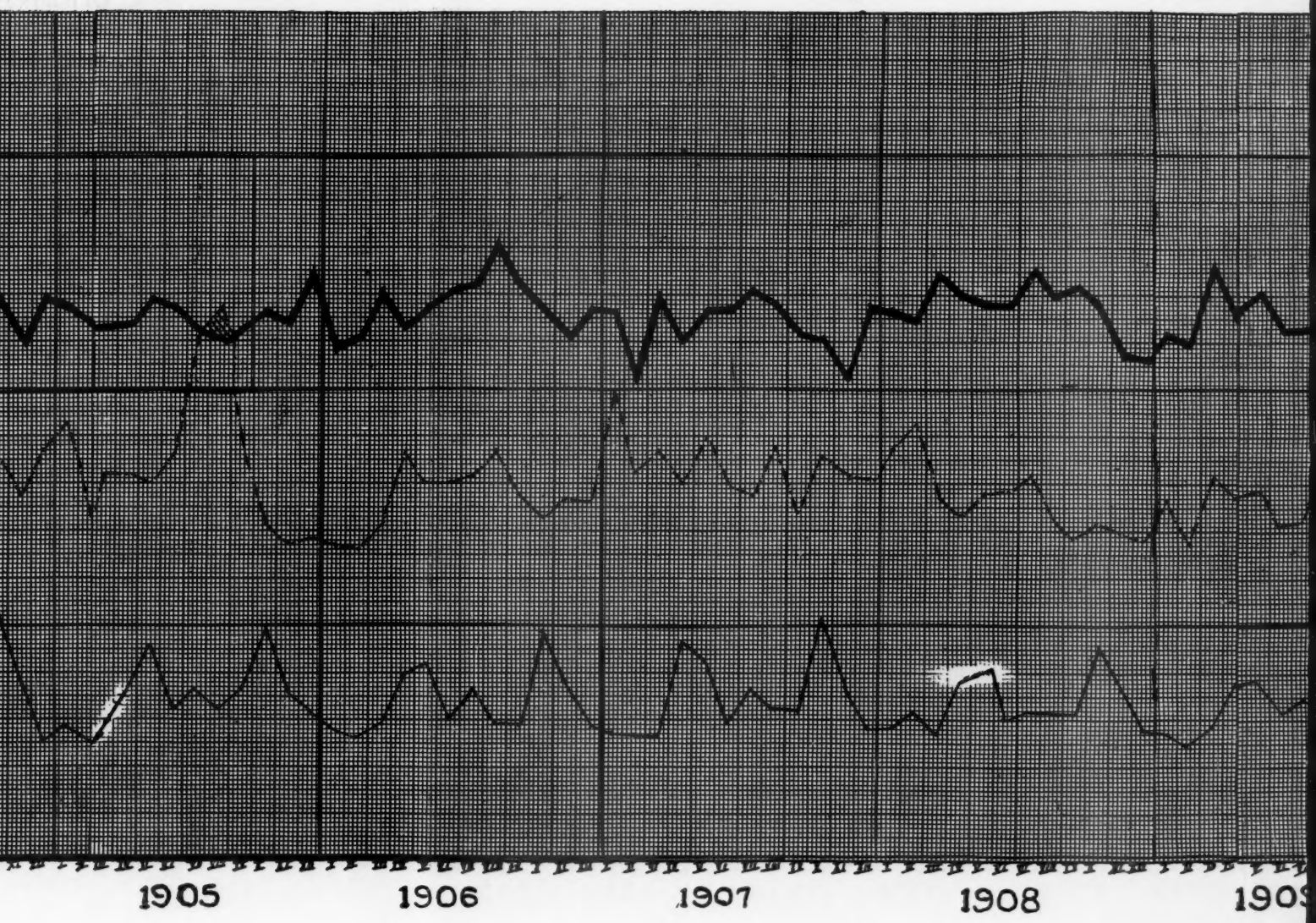
1905
1906
1907
1908

TUBERCULOSIS IN GERMANY

HAVEN EMERSON

At the request of the American Friends Service Committee, the "Quakers," I made a brief but intensive study of the condition of health, hunger and disease among the children of Germany in December, 1923, and January, 1924. In the course of these observations, made in eight large centres of population widely scattered throughout Germany, many opportunities presented themselves for learning of the present status of tuberculosis, as to incidence, death rate, facilities for control and treatment, and the clinical forms of the disease, not only among children but at all ages. This communication is based upon personal observations in hospitals and clinics and in the homes with visiting nurses, and on the study of original records of health departments, private health agencies and other statistical offices of the Reich and the cities of Berlin, Breslau, Dresden, Munich, Frankfort a M., Cologne and Coblenz and the district of Opladen.

A few general factors require statement before the significance of the present situation can be fully grasped.

During the fifteen years prior to 1914 the death rate from all forms of tuberculosis fell 35 per cent for Germany as a whole, from 219 per 100,000 population in 1899 to 142 in 1914. During the years 1914-1919 this death rate increased 50 per cent from 142 to 212 per 100,000. During the years 1920 and 1921 there was a considerable reduction in this rate following the epidemics of influenza which occurred in waves at the same times as in the other countries of Europe and in the United States. Beginning in 1922 and continuing through 1923, and apparently at an increasing rate with each succeeding quarter of the year, there again developed an increase in the general tuberculosis death rate (chart B).

The use of fluid milk in the cities of Germany has been so restricted since 1914 that few children over 4 years of age have had any, and for considerable periods in 1918 and 1919 and in 1922 and 1923 the amounts available in the cities, and even among many of the suburban and rural population groups, have been so insufficient that few children except those under $2\frac{1}{2}$ years of age have had milk.

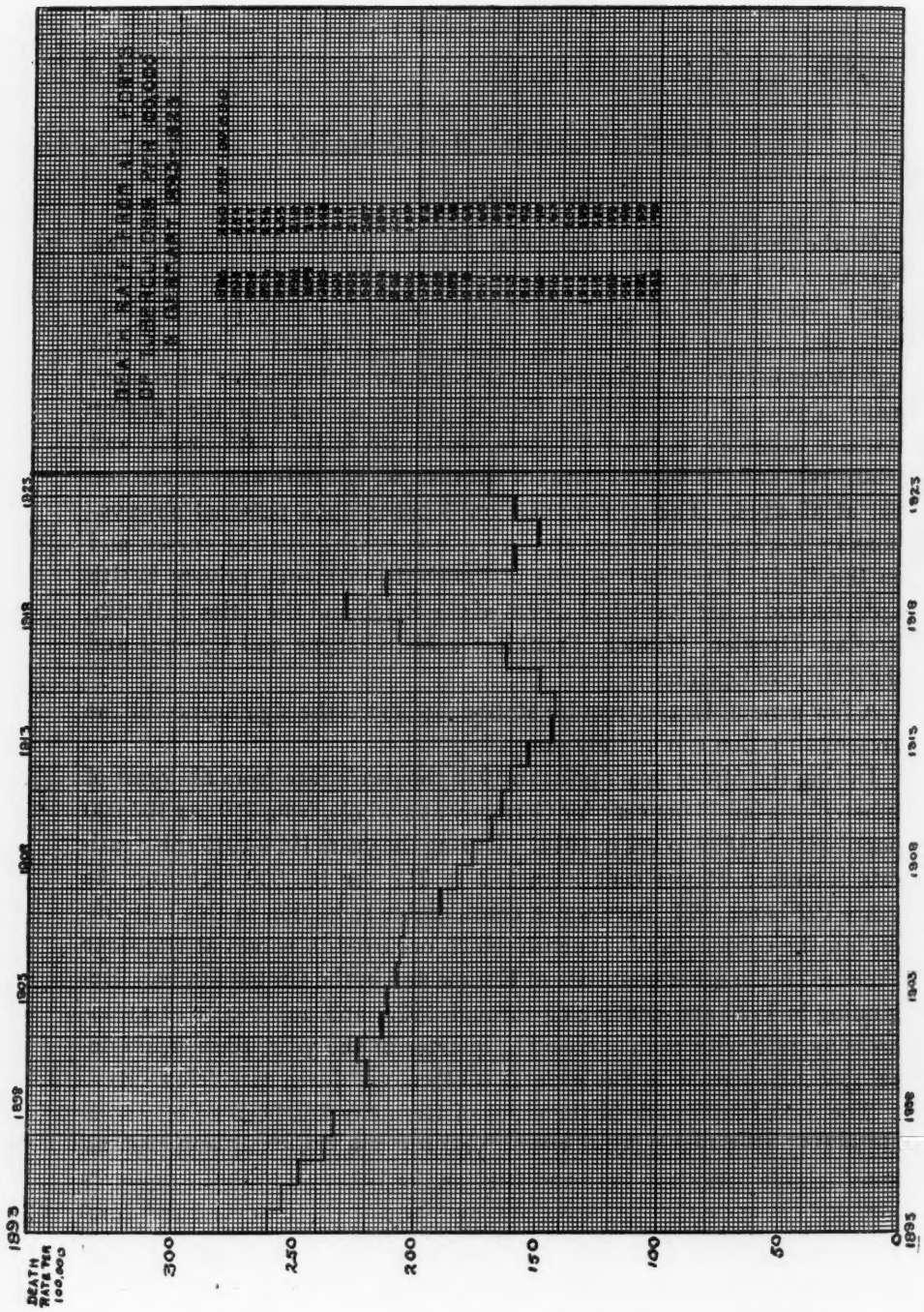

CHART B. DEATH RATE FROM ALL FORMS OF TUBERCULOSIS PER 100,000 POPULATION IN GERMANY, 1895–1923

Since 1914, there has been little or no housing construction, partly because of the removal of all incentive to provide housing, by the laws which reduced the rentals to a merely nominal sum and prevented eviction for nonpayment of rent, and partly because of the diversion of capital, labor and materials to war and the attempts to develop production for postwar commerce and industry.

Since 1922 widespread unemployment has been continuous, and increasing in amount, until at present in the cities the proportion of the population which has no means of support except from the government unemployment dole constitutes from 15 to 40 per cent of the total. During this same period the value of personal savings, investments and insurance funds has been so reduced as to provide almost nothing for relief, support or care in sickness, old age, nonemployment or industrial accidents, among wage-earners and those of the professional and middle class equally.

The poverty of the government has caused the closing of many public institutions, preventoria, hospitals, tuberculosis sanatoria, day camps, day nurseries, orphanages, etc., which formerly served to prevent tuberculosis by rest, feeding and protection, or to segregate active open cases of the disease from well persons and especially from children in the homes.

Relief and aid, by supplying coal, light, food, separate bed and room for those tuberculosis patients in the communicable stages of the disease at home who cannot obtain care in institutions, have been reduced almost to nothing.

Tuberculosis clinics, though diminished in number, are still functioning; and, through the aid of the public health nurses and social workers, cases and suspects are brought to diagnosis and kept under observation and such sanitary supervision at home as economic conditions permit. Reporting the disease is fairly complete.

Examination of children of school age is carried out with system and thoroughness. The reports of incidence and deaths are analyzed, as for many years past, according to age, sex, form of disease and distribution, to permit of reliable comparison.

The following official report by Professor Krautwig, the health officer of Cologne, to the city government on January 2, 1924, gives as briefly and effectively as possible the conditions which I found to prevail in all the cities visited during my trip:

CHART B. DEATH RATE FROM ALL FORMS OF TUBERCULOSIS PER 100,000 POPULATION IN GERMANY, 1895–1923

The records show the increase of tuberculosis mortality resulting from war conditions, the fall in the death rate with the improvement of nutrition following the war, and the sharp rise again of the tuberculosis rate in the first half-year of 1923 which quite obviously stands in a close relationship with the depreciation of living conditions and especially of the conditions of nutrition throughout the large groups of the population in the last year.

If one studies deaths from pulmonary tuberculosis particularly, it appears that the greatest increase in tuberculosis deaths is in the age groups 10 to 20 years and 20 to 30 years. There died from pulmonary tuberculosis in 1913, in the age group, 10 to 20 years, 75 persons, but in this age group, 127 died in the first 10 months of the year 1923; in the age group, 20 to 30 years, in 1913, 184 persons died from pulmonary tuberculosis, while in the first 10 months of the year, 1923, there were 286 deaths in this group.

During 1913 one out of every 9 deaths from pulmonary tuberculosis was of persons in the age group, 10 to 20 years, while in the year 1923 one out of every 7 deaths from tuberculosis was in this age group. Observations of the city physicians working in the tuberculosis clinics support the above statements. They note particularly a striking increase of new severe cases of pulmonary tuberculosis especially in young persons.

Among children of school age in the last year there were found by the school physicians and at the clinics many severe cases of tuberculosis of the skin, eye and lymph nodes. Comment has been made also by several of the school physicians on tuberculous diseases of other organs, especially the increase of lupus which was formerly rarely found among school children.

The increase of the tuberculous diseases, especially of severe active pulmonary tuberculosis in the communicable stage, is to be thought of in relation to the unfavorable condition of living places which are so commonly overcrowded, making isolation of the well from the sick for the prevention of infection usually impossible. While during the prewar period all infectious cases of tuberculosis were almost uniformly provided with a separate room, it is impossible to give the sick their room separated from the healthy member of the family in about half of all the cases, and the lack of space in the home for an additional bed makes it impossible in one-fifth to a quarter of all cases to provide the sick with a separate bed.[1]

[1] Die Aufstellung zeigt die Zunahme der Tuberkuloseerkrankung infolge der Kriegsverhältnisse, das Absinken der Sterbeziffer mit der Besserung der Ernährungsverhältnisse nach dem Kriege und den deutlichen Wiederanstieg der Tuberkulosetodsziffer im ersten Halbjahr 1923, der ganz offenbar in engster Beziehung steht zu der Verschlechterung der Lebenshaltung, insbesondere der Ernährung weitester Bevölkerungskreise im letzten Jahre. Betrachtet man die Zahl der Sterbefälle an Lungentuberkulose gesondert, so fällt auf, dass die stärkste Zunahme der Tuberkulosetodesfälle die Altersgruppen von 10–20 und von 20–30 Jahren betrifft. Es starben nämlich an Lungentuberkulose im Alter von 10–20 Jahren 1913, 75, in den ersten 10 Monaten des Jahres 1923 aber schon 127; in der

It is obvious from this that the great increase in tuberculous diseases is not to be considered a matter only of temporary importance but as likely to have an effect for a considerable period in the future on the health of the nation because of the increased spread of infection.

From the nature and brevity of my trip through Germany from place to place it must be obvious that complete statistical reports meeting the best standards for the presentation and analysis of vital statistics could not be obtained. The facts that I learned, so far as they deal with tuberculosis, can be properly grouped under

1. General death rates, sick rates, birth rates and incidence of tuberculosis in Germany as a whole and for certain specified areas.

2. Per capita consumption of milk in the larger cities of the country.

3. Housing, clothing, and feeding.

4. Restriction in public service of hospitals, sanatoria, etc.

5. The conditions among school children.

1. GENERAL DEATH RATES, SICK RATES, BIRTH RATES AND INCIDENCE OF TUBERCULOSIS IN GERMANY AS A WHOLE AND FOR CERTAIN SPECIFIED AREAS

The general tuberculosis mortality rate throughout Germany has been increasing for the past two years, each quarter of the years, 1922 and

Altersgruppe von 20–30 Jahren 1913, 184, in den ersten 10 Monaten dieses Jahres aber schon 286. Während 1913 von den an Lungentuberkulose Gestorben jeder neunte im Alter von 10–20 Jahren stand, fiel schon jeder siebte in diese Altersgruppe. Hiermit stimmen auch die Beobachtungen überein, die von Seiten der Stadtärzte an der Fürsorgestelle für Lungenkranke gemacht werden: sie berichten übereinstimmend über eine erhebliche Zunahme frischer schwerer Tuberkuloseerkrankungen, gerade besonders bei jugendlichen Personen. Im Schulalter wurden in letzten Jahre von den Fürsorge- und Schulärzten sehr viele schwere Fälle von Skrofulose, Augen- und Drüsentuberkulose gesehen. Von Tuberkuloseerkrankungen anderer Organe wird von einzelnen Schulärzten besonders auf wiederholtes Auftreten von Hauttuberkulose (Lupus) hingewiesen, die sich sonst bei Schulkindern nur selten findet. Die Zunahme der Tuberkuloseerkrankungen, besonders der schweren ansteckenden Erkrankungen an Lungentuberkulose ist um so bedenklicher, als infolge der ungünstigen Lage auf dem Wohnungsmarkt die Wohnungen sehr häufig stark überfüllt sind, so dass sich häufig eine Isolierung der Gesunden von den Kranken zur Vermeidung der Ansteckung nicht durchführen lässt. Während in Friedenszeiten alle ansteckenden Tuberkulösen ein eigenes Bett und in den allermeisten Fällen auch ein eigenes Zimmer für sich hatten, ist es heute in annähernd der Hälfte der Fälle nicht mehr möglich, die Kranken in einem eigenen Zimmer von ihren gesunden Familienangehörigen abzusondern, und in bis 1/4 der Fälle ist es nicht einmal möglich, die Kranken in einem eigenen Bett schlafen zu lassen, da Raummangel die Aufstellung eines weiteren Bettes verbietet. Man sieht daraus, dass die starke Zunahme der Tuberkuloseerkrankungen nicht nur für den Augenblick sehr bedenklich ist, sondern auch durch die erhebliche Ausdehnung der Ansteckung mit Tuberkulose noch in weiter Zukunft nachteilige Folgen für die Volkesgesundheit bringen wird.

1923, showing a higher tuberculosis rate per 100,000 than for the corresponding quarter of the preceding year.

In 46 of the large cities of Germany with 100,000 population or over, representing a total population of 17,000,000, the general tuberculosis death rate for the first quarter of each year rose from 190 per 100,000 in 1921 to 197 in 1922 and 208 in 1923.

In 1913 the tuberculosis death rate for Germany was 157 per 100,000 and in 1921, 158. It will be recalled that in Finland, for a short period after the famine in the year 1868, there was a reduction of the tuberculosis death rate followed quickly by a considerable rise in the rate, which continued for ten years. The causes of the increase in tuberculosis death rates in Germany in the past two years are widespread lack of nutrition, clothing and heat and the limitation of housing, which have reduced bodily resistance and facilitated the development and reactivation of open tuberculosis.

TABLE 1

YEAR	FIRST QUARTER	SECOND QUARTER	THIRD QUARTER	FOURTH QUARTER	TWELVE MONTHS
1921	181	158	122	135	149
1922	182	180	131	144	159
1923	208	191	147	152	170

The mortality rate from tuberculosis among women during the war period showed a rise, but the increase among the men occurred later and was of slighter degree, while the reduction of the rate for women for 1920 and 1921, following the influenza epidemic and more favorable economic conditions which prevailed during those years, lagged behind the reduction in the tuberculosis death rate for men. At the end of 1921 the advent of renewed economic distress brought on an increase in tuberculosis mortality of both sexes, which has continued uninterrupted up to the present time.

While there is no wholly accurate record of tuberculosis incidence, the experience of clinic and hospital physicians was fully confirmed by personal study of outpatient records and by the census of wards during the time of my visit. In the year, 1923, there was an increase of 29 per cent in attendance at the tuberculosis clinics in Berlin as compared with the experience of 1922. It will be recalled that in this country there was a marked increase in tuberculosis clinic attendance in the first few years after the war, but in the United States this was accomplished by

a fall in the percentage of patients applying who were found to have active tuberculous diseases, whereas in Germany the experience with this rise in 1923 has been that there is a constantly higher percentage of applicants who show advanced and active open tuberculosis of the lungs.

Tuberculosis accounted for the greatest increase among the causes of death in the years, 1913 to 1919, during which time the incidence and mortality of acute communicable diseases throughout the country showed a decrease, with the exception of influenza, typhoid fever and dysentery. The same can be said of the period 1921–1923.

In the population of 46 cities of Germany there was in 1922 as compared with 1921 a decrease of 16,754 living births and an increase of 28,876 in the number of deaths. The experience of these cities as regards tuberculosis is shown in tables 2, 3 and 4.

In table 5 it will be seen how in Old Berlin there have been, since 1921, fewer births and, therefore, deaths under 1 year for corresponding months of the respective years, while deaths from all forms of tuberculosis and at all ages increased.

Chart C is based on table 5. It shows the progressive deficit developed by the excess of deaths over births since the third quarter of 1921 and the change in the relation of deaths under one year of age to the deaths from tuberculosis at all ages and from all causes, in which it is seen that since the first quarter of 1922 the deaths from tuberculosis have been more numerous than infant deaths, whereas previous to that date the reverse was the case.

In the central districts of Old Berlin the tuberculosis death rates per 100,000 of the population at all ages were (year 1913) 156.8, (1920) 149.6, (1921) 151.2 and (1922) 183.4.

Incomplete reports for 1923 indicate that the rates for that year exceed those of any year since 1913 for these age groups. The marked improvement in 1920 over that in 1919 is quite clear and reflects the relative excellence of nutrition and economic conditions in general in 1920.

In 1913 the tuberculosis death rate in Prussia per 100,000 was 158.1 for the urban population and for the rural districts 116.5. In 1919 for Prussia as a whole the tuberculosis death rate was 218.0; for the urban population 271.6 and for the rural 168.4.

A special report to the Ministry of the Interior from the Landesgesundheitsamt of Saxony of December 4, 1923, gives a trustworthy gen-

TABLE 2

Deaths from all forms of tuberculosis in German cities of 15,000 population and over (about 350 districts) in the first six months of each year

YEAR	POPULATION	NUMBER OF DEATHS (FIRST 6 MONTHS)	DEATH RATE PER 100,000 POPULATION (FIRST 6 MONTHS)	DEATH RATE PER 100,000 FOR ENTIRE 12 MONTHS
1914	26,131,000	22,642	175	160
1919	24,798,000	41,933	344	264
1920	24,700,000	25,609	208	184
1921	25,597,000	22,795	179	158
1922	25,832,000	24,308	190	166
1923	26,110,000	26,844	207	187*

*Estimated.

TABLE 3

Deaths and death rates per 100,000 from tuberculosis in the 46 large cities of Germany

YEAR	POPULATION	FIRST QUARTER		SECOND QUARTER		THIRD QUARTER		FOURTH QUARTER		TWELVE MONTHS	
		Deaths	Death rates	Deaths	Death rates	Deaths	Death rates	Deaths	Death rates	Deaths	Death rates
1921	15,035,000	6,741	181	5,951	158	4,624	122	5,122	135	22,438	149
1922	16,432,000	7,416	182	7,404	180	5,385	131	5,920	144	26,125	159
1923	16,654,000	8,649	208	7,963	191	6,111	147			22,723*	
		[966]	[23]	[1,006]	[24]	[733]	[18]				

[Bracketed numbers: deaths under 15 years]
*In 9 months.

TABLE 4

Death rates for all forms of tuberculosis per 100,000 of population

YEAR	GERMANY	CITIES OVER 15,000	COLOGNE
1913			16.8
1914	14.2	16.1	16.2
1915	14.8	17.2	18.7
1916	16.1	18.8	19.6
1917	20.5	26.4	24.4
1918	23.0	30.0	34.1
1919	21.1	26.4	28.0
1920	15.4	18.0	19.1
1921		15.7	17.0
1922		16.6	17.1
1923			24.0

TABLE 5

Population, births and deaths (all causes) under 1 year at all ages, and from tuberculosis, all forms, in Old Berlin in January, April, July and October 1921, 1922 and 1923

	1921				1922				1923			
	January	April	July	October	January	April	July	October	January	April	July	October
Population	1,933,000	1,945,000	1,953,000	1,968,000	1,968,000	1,974,000	1,974,000	1,980,000	1,990,000	1,989,000	1,983,000	1,978,000
Births	2,642	2,485	2,290	2,012	2,171	2,109	1,845	1,597	1,754	1,736	1,530	1,370
Deaths under 1 year of age (all causes)	402	337	307	261	385	332	214	245	333	345	169	161
Deaths at all ages (all causes)	2,542	2,163	1,905	2,007	3,225	2,576	1,923	2,101	2,722	2,378	2,095	1,879
Deaths from all forms of tuberculosis (all ages)	362	312	228	225	350	356	289	252	379	403	311	265

In every month of 1923, in Old Berlin and Greater Berlin, with approximately 2,000,000 and 4,000,000 population, respectively, the infant mortality rate was lower than for the corresponding month of 1922 and the tuberculosis death rate (all forms) was higher, a paradoxical phenomenon due primarily to the falling birth rate and increase in undernourishment of all above nursing age.

TABLE 6

Death rates from all forms of tuberculosis per 100,000 males at specified age groups in Prussia

YEAR	AGE				
	0–2	2–3	3–5	5–10	10–15
1913	136	76	57	38	37
1919	238	212	139	69	65
1920	170	111	82	47	44

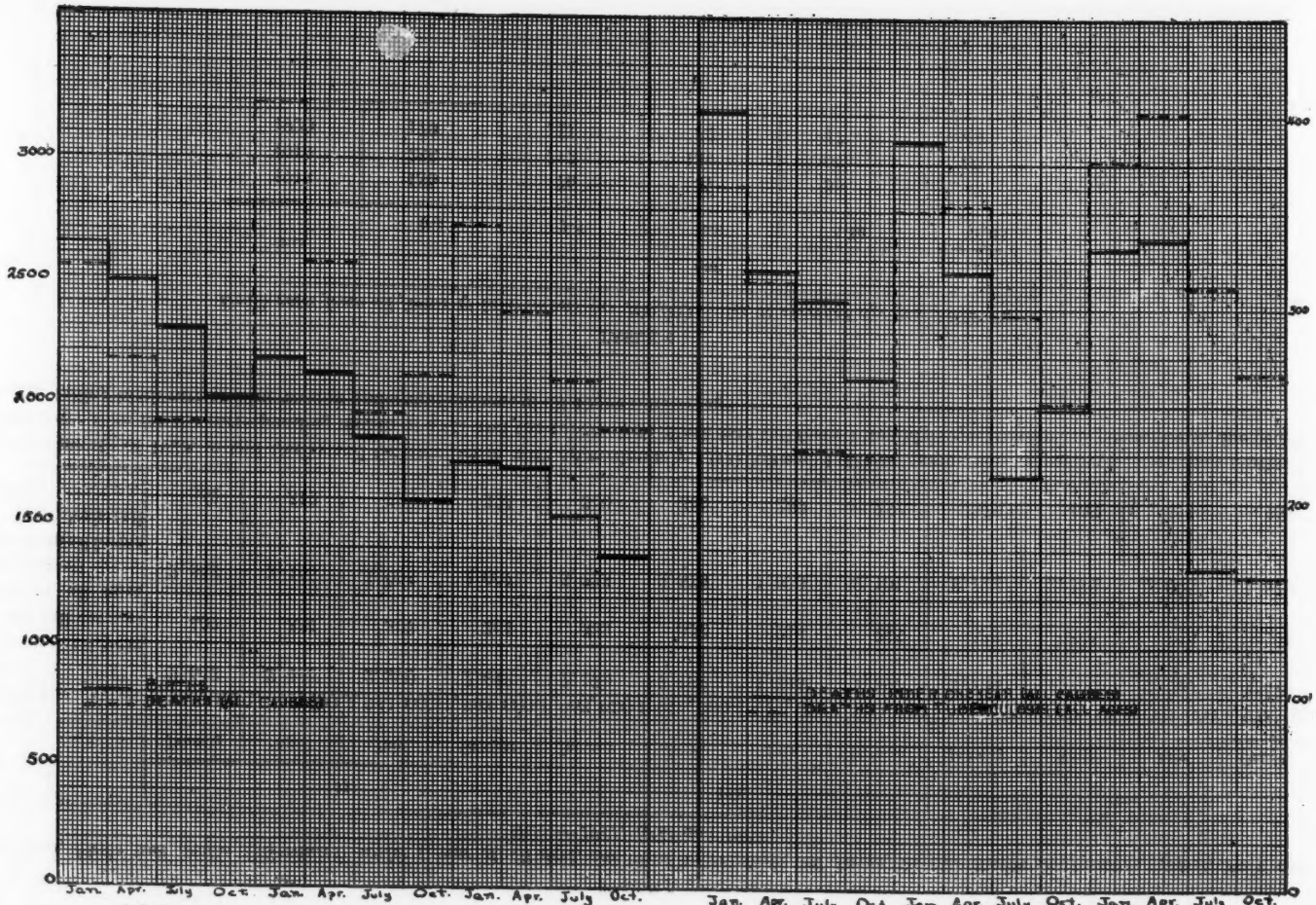

CHART C. BIRTHS, AND DEATHS FROM ALL CAUSES

DEATHS UNDER ONE YEAR, ALL CAUSES, AND DEATHS FROM TUBERCULOSIS, ALL AGES

eral picture of the population, and especially of conditions in Dresden, where it was found that in 1914, and for many years before the war, the excess of births over deaths fluctuated between 210 and 449 each month and that a similar situation developed after the war, 1919 and 1920, with an excess of births over deaths in August, 1921, of 423. By January, 1922, the reduction of the birth rate, which had fallen in the last two years almost 50 per cent, caused a monthly deficit of 53; that is, deaths exceeded births in that month by 53, and in January, 1923, there were 238 more deaths than births in Dresden. This is typical of the situation in other cities of Germany, such as Leipzig and Breslau, and for Saxony and Germany as a whole. The two outstanding determining factors in the changes of the general death rate in Germany in recent years are the reduction in infant mortality, due to a rapidly falling birth rate, with the resulting diminution in the number of the population in the age group under two years from which ordinarily one-fourth of the deaths of a general population come, and the increase in the tuberculosis death rate. Lack of coal, lack of clothing and lack of food and the overcrowded living quarters are the chief material causes for these two important factors.

The seriousness of the tuberculosis situation, as seen in Dresden, consists in the fact that on top of the heavy loss of life in 1916 and 1917 among the old people, due largely to hunger, and the losses in 1917–18–19 among all age groups from more delayed results of food deprivation and from the effect of the influenza epidemic, there is a new increase in the death rate of 1922 and 1923 after the period of improvement of 1920 and 1921 that affects all age groups. There may be said to be no balance of resources in the population. Deprivation has become chronic, and there is less help available in personal and governmental resources, while the danger of the spread of tuberculosis is greater than was the case from 1916 to 1919.

In Dresden, in every district of the city there was an increase in deaths from tuberculosis in 1923, as compared with 1922, and of cases reported from hospitals, dispensaries and private practitioners.

In Dresden, as in Berlin and Munich, there has been recorded a considerable increase in the incidence of tuberculous meningitis. In the children's hospitals of Berlin, Breslau, Munich, Dresden and Frankfort, the percentage of patients under 2 years of age who were admitted for open pulmonary tuberculosis has increased from a previous experience of

Chart C. Births, and Deaths from All Causes — Deaths under One Year, All Causes, and Deaths from Tuberculosis, All Ages

5 per cent or less, over a considerable period of years, to a percentage of 20 per cent or more in 1923.

Although the increase in tuberculosis deaths in Cologne in 1923 rep-

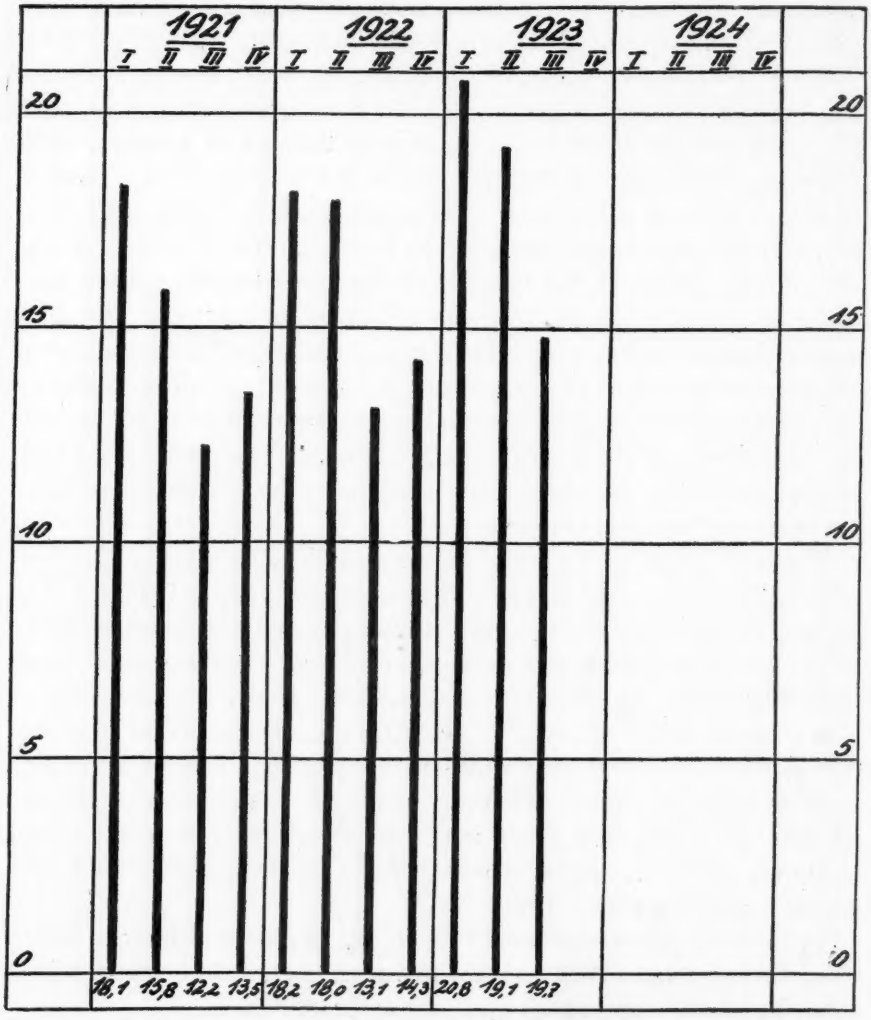

CHART D. THE DEATH RATES FROM TUBERCULOSIS PER 10,000 INHABITANTS (BY QUARTER YEARS) IN THE LARGE CITIES OF GERMANY, REPRESENTING ABOUT 17,000,000 POPULATION

resents a relatively small number of annual deaths, 174, it indicates from past experience, here and in other cities, that there were not less than 870 new open active cases of the disease, that is, five cases per death

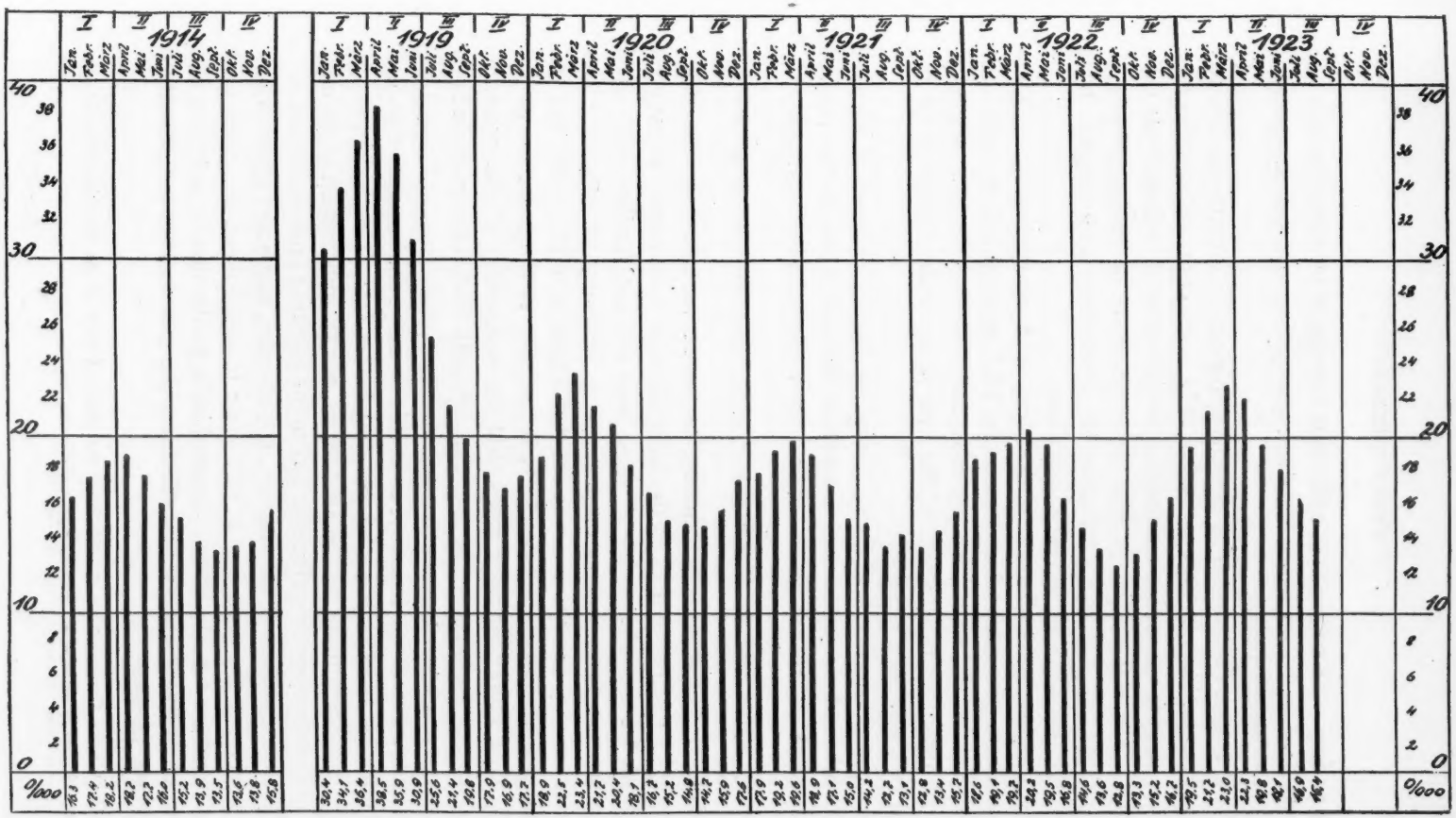

CHART E. DEATH RATES FROM TUBERCULOSIS PER 10,000 INHABITANTS (BY MONTHS) IN THE CITIES OF GERMANY WITH OVER 15,000 POPULATION (TOTAL ABOUT 26,000,000)

per annum. These serve as additional sources of infection, for the patients lived in homes where isolation, segregation and sanitary precautions are impracticable.

In Cologne, the number of persons applying for sanatorium care fell from 1948 patients in 1921 to 1407 in 1923, a situation which on its face would appear to indicate a striking improvement in tuberculosis incidence. The real reason for this, however, is the increasing poverty of the population and the diminution of sanatorium and hospital beds available for the care of the tuberculous.

In the industrial district of Opladen, with approximately 128,000 population, the tuberculosis deaths in 1915 represented nine per cent of all deaths, in 1920 fifteen per cent, and the ratio for 1923 will show a still higher figure although at the time of my visit all reports for the year had not been received.

At the *Kinderklinik* of Prof. Czerny at Berlin, children of all ages with tuberculosis represented somewhere between 5 and 10 per cent of admissions in previous years, whereas now the ratio is 25 per cent.

2. REDUCTION IN DAILY PER CAPITA CONSUMPTION OF MILK

Table 7 will express sufficiently the great reduction in the daily per capita receipts of milk in the large cities of Germany. It may be recalled, for the information of those who are not familiar with milk consumption data, that in most cities in Germany, as in most cities in this country prior to the war one-half a pint of milk a day was the usual per capita consumption.[2] It is not only in the reduction of the total milk supply for these cities that the seriousness of the situation can be seen, but also in the fact that the milk that is received contains rarely over 2.8 per cent butter fat, and commonly runs at 2.6 and 2.7 per cent, whereas in Germany, as in this country, the required standard for milk has been at least 3.5 per cent butter fat. This is due, not to neglect of precautions by the authorities, nor to adulteration of the milk by the producers or distributors, but to the fact that farmers are not now able to buy, outside of the country, the oil cake, meals and grains which they have, in the past, had to rely upon to supplement the green food and roughage for the cattle. Annual milk production in Germany fell from an average of 2,200 or 2,450 litres per cow in 1914 to 1,500 litres per cow in 1923.

[2] Per Capita Consumption of Milk from the Point of View of the Health Officer, Haven Emerson, *Am. Jour. Public Health, April, 1924, xiv, no. 4.*

3. SHORTAGE OF CLOTHING, HOUSING AND FOOD

The extent of overcrowding is difficult to express accurately, but observations, such as the following report on the conditions of 1286 school children in Chemnitz, were borne out by personal visits and inquiries in a hundred homes in the cities visited.

On November 8, 1923, among 1286 children, the entire school enrollment of one school district representing sections of all classes of the population, 580 children lived in homes where each person had a separate bed and 706 were from homes where two or more persons shared a bed. In these homes there were 63 bedrooms in each of which 6 persons slept, 30 in which 7 persons slept, 10 with 8 persons, 5 with 9 and one with 10 persons.

TABLE 7

CITY	POPULATION 1923	QUARTS OF MILK USED DAILY		PRICE PER QUART IN CENTS 1923
		1913	1923	
Berlin	4,000,000	1,180,000	135,000	7½
Breslau	560,000	112,470	43,450	7½
Dresden	610,500	135,000	25,200	8
Munich	690,000	230,400	13,500	7½
Frankfort a M.	515,000	225,000	9,000	10
Cologne	70,400	225,000	3,600	12
Coblenz	62,000	*	*	12

*Records incomplete; daily amount, 1923, one-half amount available 1922.

An excellent analysis of the causes of the increase in tuberculosis mortality in Germany up to 1920 will be found in the *Zeitschrift für Tuberkulose, May, 1921, xxxiv, 228* (Abstract in AMERICAN REVIEW OF TUBERCULOSIS, July, 1922, vi, Abstr., p. 144) by M. Kirchner, in which he emphasized the rôle of occupation, housing and food as the essential factors in operation. In his discussion of the housing shortage Kirchner discloses conditions which, though serious at the time of his writing, have had no relief since then and are now even more aggravated by the continued economic depression.

Housing conditions: According to the governmental statistics for Berlin for May 31, 1918, for every 1000 dwellings the following living arrangements prevailed:

Workroom only.....0.35
Kitchen only.....17.5 } 17.85

1 living room, no kitchen	64.0	402.7
1 living room, with kitchen	338.7	
2 living rooms, no kitchen	3.0	343.9
2 living rooms, with kitchen	340.9	
3 living rooms, no kitchen	0.68	114.2
3 living rooms, with kitchen	113.5	
4 living rooms, no kitchen	0.15	60.45
4 living rooms, with kitchen	60.3	
5 living rooms, no kitchen	0.04	28.34
5 living rooms, with kitchen	28.3	
6 living rooms, with kitchen	14.2	21.4
7 living rooms, with kitchen	7.2	
8 living rooms, with kitchen	3.7	9.1
9 living rooms, with kitchen	2.0	
10 living rooms, with kitchen	1.2	
Over 10 living rooms, with kitchen	2.2	

In Berlin, therefore, 40 per cent of the dwellings consisted of only living room with or without kitchen; 17 per cent of 3 to 4 living rooms with or without kitchen; a little over 4 per cent of 5 to 7 living rooms and only 1 per cent of more than 7 living rooms. In 1905, of 522,558 dwellings in Berlin there were 1.3 per cent with no heated rooms, 47.6 per cent with one, 34.2 per cent with two, 11.1 per cent with three, 4.3 with four, and only five or more heated rooms. Hence, in 49 per cent of all these dwellings there was a tuberculous person who had to share the only heated room with the others. During the war these conditions were aggravated (1) because of increase in city population which followed the influx necessitated by the manufacture of arms and munitions, (2) because of the decrease in the building of dwellings due to scarcity of building materials and of skilled workmen, and (3) because of the shortage of fuel. The decline in building projects is seen from the following Berlin statistics:

	DWELLINGS		OTHER BUILDING WITH DWELLINGS		TOTAL DWELLINGS	
1910	212		31		5930	
1911	220		31		6084	
1914	80		21		1817	
1915	36		12		733	
1916	12	130	2	40	203	2773
1917	1		3		15	
1918	1		2		5	

According to normal building activities, instead of only 2,773 dwellings being erected during the war, 30,035 should have been erected.

The worst instances among the 1286 children of Chemnitz were those where in two rooms 11 persons of the family occupied 4 beds and in two rooms 7 persons of the family occupied 2 beds.

As to the clothing and feeding of these children, 321 either had no shoes (20) or had shoes so torn or worn as to offer no protection against the weather; 1026 had coffee and bread before going to school (*erste Frühstuck*), 92 had soup and 168 had nothing, and 238 brought no school lunch (*zweite Frühstuck*) and among these were most of the children who had had no first breakfast. Of the 1048 who brought a school lunch, 52 had a piece of dry bread, 919 had bread with some fat as a spread (not butter), 77 had bread and butter, and 276 had meat or fish at dinner. The rest had no flesh food in their diet.

The food supplied at home for the 18 children in whom undernourishment was most severe was as follows in 8 instances, not including the worst dietaries where food was wholly lacking several days in the week:

	NUMBER IN FAMILY
Noodles at noon, soup at night	4
Bread at noon, potatoes at night	5
Bread at noon and bread at night	8
Cornpot at noon and bread at night	6
Nothing until night, then bread and margarine	4
Potatoes with salt for supper	2

In Chemnitz, as in many other cities of Germany, the milk supply fell 75 per cent between 1914 and 1920 and 30 per cent further from the 1922 daily amount during the last half of 1923.

A quarter of the population depends upon the public dole (10.5 gold marks, or $2.50 a week, for a man and wife and two children) for support, all of which is spent in food, coal, soap and a nominal rent, the food cost representing 85 to 90 per cent of the weekly family budget. In Dresden it is recorded that there are 35,000 married persons who have no independent homes and are living with their parents.

Insufficiency of clothing of children is not obvious upon the street, as there is still the same care in mending, darning and repair of outer garments as has always been characteristic of the German mothers, but absences from school in cold and stormy weather are very numerous and the continuous housing of children for weeks at a time because of unsuitable clothing is everywhere observed.

These facts are difficult to express convincingly or statistically, but some idea of conditions can be obtained from the reports of the school physicians who carried out an inquiry in November, 1923, in the matter of clothing, feeding and home conditions of the children all over Germany.

They found such facts as the following which are reported from Munich: 40–50 per cent of school children possess only one shirt; 75 per cent of the children have no shoes suitable for snow and rainy weather; 20–30 per cent of the children have no leather shoes; 10–20 per cent are wearing shirts meant for adults; 30–40 per cent have no stockings; 50 per cent have no overcoat; 30–70 per cent lack some essential of clothing; 60 per cent are louse infested; 30 per cent have no separate beds.

4. REDUCTION IN HOSPITAL, SANATORIUM AND OTHER FACILITIES FOR THE CARE OF TUBERCULOSIS PATIENTS, ETC.

Of 9,000 beds in hospitals and sanatoria for tuberculosis, 20 per cent have already been put out of commission because of the limitation of government and private resources for their maintenance, and early in 1924 the reduction will reach 40 per cent of the total accommodations of two years ago.

In Saxony, alone, the reduction in state institutions for tuberculosis has been 12.4 per cent in the last year, and hospital beds for the tuberculous have been reduced between 30 and 40 per cent in most of the large regions of the country, with a still greater reduction of facilities for preventoria and convalescent care. In Berlin and Prussia, as a whole, there has been a reduction of 25 per cent in the institutions for infant and child welfare.

In the beginning of 1923, 15 per cent of the homes for nurslings and almost 50 per cent of the beds in infant shelters throughout Germany had been closed, and in Berlin 93 of the kindergartens and 8 of the children's shelters had been closed in 1922. There remain in 1923 only 6 of the 28 children's shelters which were in operation in 1918. Four hundred beds in municipal preventoria for pretuberculous children in Berlin were closed in the last year.

Even the institutions which still operate for the care and treatment of tuberculosis in children find it impracticable to carry out open air treatment for the disease in the cooler months of the year, since the food allowance for the children is so low that their undernourishment con-

tinues to be a serious handicap and evidently contributes to the high incidence of bronchial diseases and acute catarrhal processes of the respiratory tract, which persist much longer than is the case in well-nourished children. Exposure of such children to the cold air, even in sunny weather, does not result in improvement of their condition.

Whereas in 1920 only 6.6 per cent of the tuberculous patients were discharged from Hohwald, a sanatorium outside of Dresden, as unfit to work because of the lack of sufficient rest and convalescence from tuberculosis, in 1923 there were 17 per cent of the discharged patients who were unfit to work at the time of leaving the sanatorium. Of similar importance is the fact that in 1920 only 1 per cent of the tuberculous patients were discharged unimproved whereas in 1923 11.8 per cent were unimproved. Again, in 1920 only 1.4 per cent of the patients of this sanatorium were discharged because they were unable to pay for further care, whereas in 1923 this group of discharges had risen to 15.6 per cent.

At the Virchow Hospital in Berlin, where the regular ward diet included previously one litre of milk a day, 1500 grams of meat a week, 50 grams of butter a day and 2000 grams of bread, the restrictions in resources have forced them to cut down these elements of regular diet to 300 grams of milk a day, 600 grams of meat a week, 15 grams of margarine a day and 1800 grams of bread a day.

In this hospital they have to provide, for advanced cases of tuberculosis, five units of 60 beds each, where there were formerly needed only two, the closing of the sanatoria and other places for the care of tuberculosis in its early stages having forced patients into homes and then into the hospitals of the cities, where general hospitals are still operating, though not to full capacity.

A number of brief histories, taken of the patients in these special tuberculosis units of the Virchow Hospital, showed that most of them had developed their disease since the war and came from families where there were other active cases of the disease, with whom they had been in necessarily close contact as attendants or caretakers of the sick.

In 1922 in Prussia, 22 public and 23 private hospitals, with a total of 2459 beds, were closed, and still more hospitals with considerable increase in the number of beds were discontinued in 1923. All the private bath establishments but one in Prussia were closed, and 90 per cent of those throughout Germany have been discontinued because of lack of paying patronage.

5. CONDITIONS AMONG SCHOOL CHILDREN

It was reported, at a conference of school physicians assembled from all parts of Germany in November, 1923, that there had been an increase of 16 per cent in open tuberculosis among school children in the first 9 months of 1923. There has been an increase in the general tuberculosis death rate among children in Berlin, under 14 years of age, from 41 to 106 per hundred thousand children of these ages. Thirty per cent of the boys and twenty-nine per cent of the girls of legal working age on leaving school failed to receive certificates of physical fitness for work because of their undernourishment.

Three per cent of the school children in Germany are found to have active pulmonary tuberculosis, and from 25 to 30 per cent of the school children show definite signs of tuberculous infection without active pulmonary processes.

The percentage of children found by the school physicians to be unfit to continue school attendance in German cities has increased from 2.1 per cent in 1913 to 10 per cent of the school attendance in 1923.

In Greater Berlin the increase of deaths from tuberculosis of all forms, among those under 15 years of age of both sexes, was 30 per cent between 1912 and 1922; for children under one year the increase was 50 per cent, while during the same period the increase for those 15 years and over was 10.2 per cent.

Clinical tuberculosis in an active stage of the disease is found commonly in from 2 to 3 per cent of the school children of all ages, as shown in official reports from many widely scattered cities and small suburban and industrial districts.

It is found in the poorer parts of large cities that 50 to 75 per cent of the children show enlarged lymph nodes and scrofulosis. Anemia of severe grade is found prevalent wherever tests are made, while colds and infections, due to exposure because of inadequate clothing and shoes, are more numerous than ever and of longer duration.

Retardation of height and weight, corresponding to about two years of normal growth, is almost universal, at least among city school children, in whom height is less by two inches and weight by 10 pounds than in normal healthy children of similar age.

In 1923, of 2000 children representing 4 age groups, 1–2, 6 years, 11 years and 14 years of age, the body weight of boys in all instances was less by 0.5 to 1.0 k. than the weights of boys of similar ages in 1919, and

from 3.7 to 8.6 cm. less in height than the normal for these ages as estimated by the Pirquet-Kammerer scale for height and weight for age.

Among girls of these age groups the deficit in weight as compared with 1919 experience was greater than among boys. In the matter of body length similar though less marked deficits were shown between the 1919 and the 1923 measurements of the respective age groups, and the deficit in length in 1923, as compared with the so called normal scale, amounted to from 1.5 to 12.4 cm.

TABLE 8

Body weight in kilograms and height in centimetres among 2,000 children in the City Orphanage of Berlin

	NORMAL	1919	1922	1923
Body weight: Boys				
1–2 years	12.7	9.5	9.9	9.0
6 years	20.5	16.1	17.1	16.6
11 years	32.5	27.2	26.1	25.9
14 years	41.0	33.2	32.1	32.4
Body weight: Girls				
1–2 years	12.2	8.9	8.8	8.4
6 years	19.0	15.9	17.4	16.1
11 years	29.0	25.6	26.1	25.9
14 years	43.0	26.2	36.9	35.3
Body length: Boys				
1–2 years	85.0	72	73.2	73.5
6 years	109.0	99	102.8	101.6
11 years	135.0	128	136.7	125.8
14 years	151.0	140	136.1	138.6
Body length: Girls				
1–2 years	84.0	75.8	72.3	71.1
6 years	107.0	100.6	102.9	102.9
11 years	133.0	126.8	128.4	126.0
14 years	152.0	140.9	144.8	139.4

The preceding table 8 expresses with reasonable accuracy the extent to which depreciation in child physique occurred between 1914 and 1919, the partial recovery during the favorable years of 1920 and 1921, and the further depreciation since 1922. With this there has been anemia, usually less than 70 per cent hemoglobin, and in a large proportion of the school children as low as 50 per cent hemoglobin, with a quality of mus-

culature and general nervous debility, expressed in fatigue postures of trunk and feet, lack of endurance even for the abbreviated school day, and a high incidence of exhaustion, dizziness, headaches and nervousness in school periods.

Among the children from 3 to 4 years of age admitted to the city orphanage in Berlin one-third were found to have active pulmonary tuberculosis in 1923. The incidence of active tuberculosis among children under 1 year of age admitted to the same institution varied from a rate of 3.7 per cent in 1913 to 3 per cent in 1921, and it rose in 1922 to 9.7 per cent.

In Cologne tuberculosis in school children was formerly rare, showing an incidence of from 1 case in 20,000 up to 1 case in 12,000 school children, whereas in 1923 the incidence was 1 to 500 children.

In Dresden, the school dispensary physicians report an increase in tuberculosis in the early age groups since 1922, and an increase of tuberculous infection of the bronchial lymph nodes and of tuberculous diseases of the skin and eye.

Of 6,000 school children in Coblenz 6.3 per cent were tuberculous, either with an active type of the disease or of a degree requiring attendance at the tuberculosis clinic, and sufficient to excuse them from school attendance because of their condition. The limitation of facilities in this city is shown by the fact that only 50 cases of tuberculosis, whether children or adults, could be brought under sanatorium or institutional treatment during the past year.

In the town of Furth, Bavaria, of the 721 children of the first school grade 515 had swellings of the lymph nodes of the neck and jaw. An entirely comparable condition was found among children of the eighth grade. In the schools of this district shower baths, school polyclinic and midmorning milk lunches had to be discontinued for lack of funds.

In the Schönberg district of Berlin in 1913, 8.1 per cent of the children leaving school were found to have active tuberculosis or were classed as suspects, whereas in 1922 the percentage of such children was 15.

Active cases of tuberculosis in school children of the Neuköln district of Berlin were found, in 1914, in 1.5 per cent of the children; in 1920, 1.2 per cent; in 1921, 2.5 per cent; and in 1922, 3.2 per cent.

In the children's polyclinic of Berlin, 1 per cent of all patients admitted in 1923 had tuberculosis, while in 1922 the percentage was 4.8 per cent.

The death rate from tuberculosis under 14 years of age in Berlin, in 1913, was 0.41 per thousand living at this age group and in 1922 it was 1.06.

In the Berlin City orphanage all admissions over 6 years of age in 1922 gave a positive Pirquet test and a large proportion of those over 3 years of age reacted similarly. The importance of the increasing incidence of tuberculosis among school children becomes increasingly clear when one recalls the fact that the same school rooms, which now contain from 50 to 60 children each, formerly held only 35 to 40 children.

While it is apparent that bodily vigor of children has been seriously depreciated during recent years in Germany, by the long continued and, at times, extreme limitation in the quantity and quality of foods known to be desirable and indispensable for normal growth and development in childhood, we have no measure of the reduction in specific susceptibility to infection with the tubercle bacillus, much as we may believe in this as a major factor in the spread of the disease.

What is however quite as obvious and, I should say, apparent with more convincing evidence, is the intimacy, continuity and massiveness of infection of both children and adults, made possible and, one may properly say, inevitable by the conditions of housing, and the breakdown of many of the facilities and resources, individual and administrative, for the segregation of the sick tuberculosis patient from well members of the family.

The increase of the death rate from tuberculosis in all ages of the population gives but a faint and crude indication of the increase in the prevalence of infection or of the extent of outspoken tuberculous disease. There are being reproduced in Germany now, as there were between 1916 and 1920, conditions which favor a prevalence of the disease similar to that of thirty years ago.

Such experiences tend to confirm an impression, expressed in a previous publication,[3] that improvement in industrial conditions and in the standard of living of wage-earners and their families, is a more potent factor in determining the reduction of tuberculosis mortality in this country and abroad during the past thirty years than any of the specific or accessory measures employed for attack against the disease.

Germany is presenting now a picture of acute epidemic spread of tuberculosis, due primarily to uncontrollable insanitary conditions of

[3] Causes of the Rapidly Increasing Fall of the Tuberculosis Death Rate in the Last Five Years, *Amer. Rev. Tuberc., June, 1922, vi, no. 4.*

housing and lack of means to separate the sick from the well. Probably contributing to this as a very important factor is the lack of food and, in particular, the shortage in milk, butter and animal fats in the diets of children since 1914.

TUBERCULOUS REINFECTION AND THE TUBERCULIN REACTION IN THE TESTICLE OF THE TUBERCULOUS GUINEA PIG[1]

ESMOND R. LONG[2]

The experiments recorded in this paper deal with two related subjects; first, the comparative effects of tubercle-bacillus infection of the testicle in normal and already infected guinea pigs and, second, the effect of tuberculin upon the testicle of normal and tuberculous guinea pigs. In addition, a subject related to both is briefly touched upon; namely, the effect of the testicular injection of nonpathogenic, acid-fast bacilli.

It has long been felt that a method for the production of a localized, slowly progressive tuberculosis, in a cheap, experimental animal, simulating the tuberculosis of man, would be a great aid in the experimental study of tuberculosis, and particularly of its therapy. Dr. H. G. Wells has suggested to me that guinea pigs infected in one of the usual sites, such as axilla or groin, with tubercle bacilli of low virulence and reinfected in the testicle with tubercle bacilli of moderate virulence, might exhibit a fairly restricted, not too progressive tuberculosis, somewhat comparable to that of man, which would be useful in the experiments in progress at the Sprague Institute on chemotherapy. Maver and Wells (1), with the coöperation of Doctor DeWitt, have already examined tuberculous testicles of guinea pigs in their work on calcification.

M. I. Smith (2) records experiments on primary testicular infection in the rabbit, and reviews the small amount of literature upon this subject. He finds that a lesion long restricted to the testicle can be obtained in the rabbit if the human type of tubercle bacillus is used, and suggests that such a lesion is well adapted for studies in experimental therapy. This method, I am sure, will be of much use. But for extensive work it is an expensive one, in view of the high cost of rabbits in original price and maintenance, and in view, further, of their

[1] From the Department of Pathology of the University of Chicago, and the Otho S. A. Sprague Memorial Institute.

[2] Aided by a grant from the National Tuberculosis Association.

great susceptibility to acute respiratory infections. Furthermore, the tuberculosis of man will be more closely simulated by the lesion of reinfection.

The work here considered had been under way but a few days when it became apparent that the testicle is an extraordinarily sensitive indicator of the allergic condition. What was by design an experiment on reinfection became, in effect, a study of the response of a highly specialized tissue to tuberculin.

PLAN OF EXPERIMENTS ON REINFECTION

The plan of the experiments on infection and reinfection was similar to that used by Trudeau (3), Nichols (4), Paterson (5), Soper (6), Léon-Kindberg (7) and others in their work on reinfection. A number of male guinea pigs, of 350 to 550 gm., were infected intraperitoneally with 0.1 mgm. tubercle bacilli of low virulence. The Saranac Laboratory strain R1 was used. Twenty days later these guinea pigs were given an inoculation of 0.1 mgm. tubercle bacilli of moderate virulence in the left testicle, for which the Saranac Laboratory strain H37 was used. These were called *A* guinea pigs. Simultaneously, an equal number of normal male guinea pigs of similar weight were similarly inoculated with the same dose of H37. These were called *B* guinea pigs. At various intervals an *A* guinea pig and a *B* guinea pig were killed and examined, grossly and microscopically. A second series was run later, in which one group received a primary infection of R1 in the left axilla, far removed from the testicle's regional lymph nodes, and a second infection in the testicle with 0.01 mgm. of a highly virulent bacillus, while the same number of normals received testicular injection only. The bacillus used in the testicle infection I have called H301. It is one of extremely high virulence, used for these experiments only twenty days after it came out of the human body, in the first culture from sputum. These guinea pigs are called respectively *C* and *D* guinea pigs. For comparison with these, a series was studied in which a single infection of the testicle was made with the bacillus of low virulence, R1. These are called *E* guinea pigs.

Below are given the protocols of the guinea pigs of the *A*, *B*, *C*, *D*, and *E* groups. To avoid monotonous description the amount of tuberculosis in an animal is designated as follows: no tuberculosis except that of testicle; *1*+, meaning tuberculosis limited to region of injection; *2*+, meaning beginning generalized, with slight but definite tuberculosis of the spleen; *3*+, meaning generalized tuberculosis. Microscopic examination was made of most of the organs. Especial attention was given to the genitourinary system. Hematoxylin and eosin were used routinely, but with the kind coöperation of Dr. William Snow Miller, I was able to secure reticulin stains for certain specimens.

As will be noted, the term epithelioid cell is used regularly for that large mononuclear cell, variously called endothelial cell, subendothelial cell, reticuloendothelial cell, clasmatocyte, histiocyte, and by other names, in the literature. The designation seems to depend upon the environment; and in this sense for our purpose the term *epithelioid* cell, so commonly employed in the description of the tubercle, seems appropriate, even though the structures described do not resemble epithelium and in many cases do not have the characteristic architecture of a tubercle.

PROTOCOLS OF *A* AND *B* GUINEA PIGS

Reinfection in testicle compared with primary infection of testicle

Infections and death

	A guinea pigs	*B* guinea pigs
February 1, 1923	One-tenth of a milligram of R1 tubercle bacilli injected intraperitoneally	Noninfected
February 20, 1923*	One-tenth of a milligram of H37 tubercle bacilli injected into left testis	Same treatment as *A* guinea pigs
	Guinea pigs killed by illuminating gas at intervals, or dead from intercurrent infection or from tuberculosis itself	Killed by gas with an *A* mate or dead from intercurrent infection or from tuberculosis itself

* With the exception of guinea pigs A1 and B1, which received the inoculation in the testicle March 13. This lack of uniformity is due to the fact that the original plan had not contemplated an examination at the end of two days.

Necropsy findings

A1 and B1 (2 days after testicle infection, 40 days after primary infection of A1)

A1: Gas. Tuberculosis 1+. The *left testicle* is much enlarged and the tunica extremely hyperemic. The left spermatic vein is dilated. The *right testicle* is normal.

Microscopic: Left testicle (see figure 3): There is extensive necrosis of the tubular epithelium. The developing germ cells are chiefly affected. Fully developed spermatozoa are frequently spared and remain in the centre of the tubules surrounded by spermatids and spermatocytes in which the nuclei are pyknotic or do not stain at all. A ring of spermatogonia (or Sertoli cells?) in a state of pyknosis is usually seen just interior to the basement membrane. The destruction is not uniform in all tubules, some tubules seen in longitudinal section showing necrotic areas and areas which are nearly normal. There is a dense infiltration of polymorphonuclear leucocytes and a smaller number of round cells and epithelioid cells between the tubules and to a considerable extent within them. The *epididymis* is normal; the tubules are full of spermatozoa. The *right testicle* is normal.

B1: Gas. No tuberculosis except testicle infection. The *left testicle* is about normal in size. There are no abnormalities elsewhere.

Microscopic: Left testicle (see figure 4): The tubules are almost normal in appearance. The germ cells show no change. There are fewer spermatozoa in the left than right testicle (discharged?). There is a moderate intertubular infiltration of wandering cells, which include epithelioid cells, eosinophiles, polymorphonuclear leucocytes and small round cells. The *right testicle* is normal.

A2 and B2 (8 days after testicle infection, 27 days after primary infection of A2)

A2: Gas. Tuberculosis 1+. The *left testicle* is slightly enlarged and hard. The tunica is very hyperemic, and there is a fibrinous exudate at the lower pole. The *right testicle* is normal.

Microscopic: Left testicle: The parenchymatous tissue is largely replaced by a dense infiltration of epithelioid and round cells. A few greatly swollen, necrotic tubules are seen. Polymorphonuclear leucocytes are numerous in the vicinity of these tubules. Besides these the few tubules that remain are scattered, separated by the cellular infiltration, not over half normal size, and show no spermatogenesis. The cells lining the tubules resemble spermatogonia. The epithelioid cells of the infiltration are not arranged into definite tubercles. The *epididymis* is infiltrated with round cells. The tubules are full of spermatozoa. The *right testicle* is normal.

B2: Gas. No tuberculosis except testicle infection. The *left testicle* is enlarged, and the tunica hyperemic. It is larger than in A2 and not so hard. The *right testicle* is normal.

Microscopic: Left testicle: The parenchymatous tissue of half of the body is largely replaced by a dense infiltration of epithelioid and round cells. The tubules remaining in this area are decreased in size and show no spermatogenesis; they are lined by cells resembling spermatogonia. The pathological process is not sharply limited, but fades gradually into normal tissue. (*This is in sharp contrast to A2, in which spermatogenic function was abruptly destroyed by what was essentially a tuberculin reaction.*) Swollen, necrotic tubules, such as were seen in A1, are not present. The epithelioid cells of the infiltration are not oriented into tubercles. The *epididymis* is practically normal. The *right testicle* is normal.

A3 and B3 (17 days after testicle infection, 36 days after primary infection of A3)

A3: Gas. Tuberculosis 2+. The *left testicle* is the same size as the right, but hard and nodular and discolored with yellow areas of necrosis. The *right testicle* appears normal.

Microscopic: Left testicle: The parenchyma is almost completely replaced by infiltrated epithelioid cells. Round cells are not so numerous. The tubules are like those of A2, except that no swollen necrotic ones are present. The epithelioid cells are frequently arranged concentrically; the centre is often a degenerated tubule. Polymorphonuclear leucocytes are frequently found in degenerating tubules. The condition occasionally approaches suppuration. A few giant cells are present. The *epididymis* is infiltrated with epithelioid cells, occasionally aggregated into dense masses. There are few spermatozoa in the tubules. The *right testicle* is normal.

B3: Gas. No tuberculosis except testicle infection. The *left testicle* is much enlarged and adherent in its sac. The *epididymis* is especially swollen. The testicle contains a caseous nodule, 0.5 cm. in diameter. The *right testicle* is normal.

Microscopic: Left testicle: The parenchyma is almost completely replaced by epithelioid cells, which for the most part are not arranged into tubercles. Tubules are hard to distinguish. Giant cells are present, but rare. The *epididymis* is densely infiltrated with round and epithelioid cells and polymorphonuclear leucocytes. The tubules contain no spermatozoa. The *right testicle* is normal.

A4 and B4 (23 days after testicle infection, 42 days after primary infection of A4)

A4: Gas. Tuberculosis 2+. The *left testicle* is hyperemic and adherent in its sac. The left, but not the right, iliac lymph nodes are enlarged and contain yellow, caseous nodules. The *right testicle* is normal.

Microscopic: Left testicle: The parenchyma is largely replaced by wandering cells which include many fibroblasts. There are many areas of young connective tissue in which collagen

is present in parallel strands. There are also ill-defined patches of necrosis in which there is considerable karyorrhexis. Polymorphonuclear leucocytes are numerous in these areas. The tubules which have escaped are lined by undifferentiated cells and show no spermatogenesis. The *left epididymis* is normal, but the tubules contain no spermatozoa. The *right testicle* is normal.

B4: Gas. Tuberculosis 3+. The *left testicle* is adherent in its sac, hyperemic and mottled with yellow areas of necrosis. The right and left iliac lymph nodes are enlarged but not caseous. The *right testicle* is normal except for the tunica on the mesial side, which is hyperemic where it approximates the left testicle.

Microscopic: Left testicle: The tissue is densely infiltrated with epithelioid cells showing little characteristic orientation. There are areas of caseation necrosis. Giant cells are few. A very few tubules, lined by undifferentiated cells and showing no spermatogenesis, remain. There is some ingrowth of connective tissue from the tunica. The *left epididymis* is infiltrated with wandering cells, but in no place necrotic. No spermatozoa are present in the tubules. The *right testicle* is moderately infiltrated with round cells, and spermatogenesis is not very active.

A5 and B5 (24 days after testicle infection, 43 days after primary infection of A5)

A5: Gas. Tuberculosis 3+. The *left testicle* is adherent in its sac and hyperemic. The *left epididymis* is enlarged and indurated. The right and left iliac lymph nodes are enlarged and have necrotic centres; the condition is more advanced on the left. The *right testicle* appears normal.

Microscopic: Left testicle: The tissue resembles A3, but the fibrosis and suppuration are both more marked, two or three definite abscesses being present. Giant cells are very numerous. There is a marked fibrous periorchitis. The *left epididymis* is moderately infiltrated with epithelioid cells. The *right testicle* is normal; spermatogenesis is very active.

B5: Intercurrent infection. Tuberculosis 2+. The *left testicle* is adherent in its sac, deeply injected with blood, and contains many caseous nodules. One left iliac lymph node is greatly enlarged and caseous. The *right testicle* appears normal.

Microscopic: Left testicle: The body is largely necrotic through confluence of caseous areas. There is some irregular fibrosis, decidedly less than in A5. Very few tubules are recognizable. No giant cells are seen. The reaction outside the tunica is less marked than in A5. The *epididymis* is densely infiltrated with wandering cells and partly necrotic. *Right testicle:* There is marked hydropic degeneration of much of the tubular epithelium, and atrophy of the parenchyma as a whole.

A6 and B6 (31 days after testicle infection, 50 days after primary infection of A6)

A6: Gas. Tuberculosis 3+ (but less extensive than in B6). The *left testicle* is adherent in its sac and very hyperemic. The iliac lymph nodes are enlarged and partly caseous, especially the left. The *right testicle* appears normal.

Microscopic: Left testicle: There is extensive suppuration and necrosis, apparently in a tissue consisting chiefly of epithelioid cells and fibroblasts. The picture in every way suggests a marked secondary infection. A good many tubules are spared, lined by high, ragged epithelium, showing no spermatogenesis. The interstitial cells of Leydig are somewhat increased. The *epididymis* is extensively infiltrated with epithelioid cells, and the tubules are filled with polymorphonuclear leucocytes. *Right testicle:* Most of the tubules show a marked interference with spermatogenesis. Spermatogonia line the tubules and a few spermatocytes are formed, but there are very few spermatids or spermatozoa.

B6: Gas. Tuberculosis 3+. The *left testicle* is lightly adherent in its sac, and is hyperemic. The iliac lymph nodes on both sides are enlarged and caseous. The *right testicle* appears normal.

Microscopic: Left testicle: There is extensive necrosis involving the entire body, with much karyorrhexis in parts. There is some early fibrosis near the tunica albuginea. A very few atrophied tubules remain. The *left epididymis* is slightly infiltrated with epithelioid and round cells. *Right testicle:* There is extensive degeneration of the tubular epithelium. Only swollen spermatogonia are left. The *right epididymis* is normal except that the tubules contain no spermatozoa.

A7 and B7 (37 days after testicle infection, 57 days after primary infection of A7)

A7: Gas. Tuberculosis 3+ (but much less extensive than in B7). The *left testicle* is small, hyperemic and hard. The left iliac lymph nodes are enlarged but not caseous; the right appear normal. The *right testicle* appears normal.

Microscopic (see figures 5, 7 and 8): *Left testicle:* The tissue consists chiefly of young connective tissue and epithelioid cells. The latter occur in definite accumulations, often concentrically arranged and separated by fibroblasts. Atrophied tubules are seen here and there; they show no spermatogenesis. Sections stained for reticulin, kindly prepared for me by Dr. William Snow Miller, show a coarse deposition of this substance throughout the body of the testicle, especially dense where the epithelioid cells are most numerous. The same stain reveals a considerable amount of collagen. The left *epididymis* is extensively infiltrated with epithelioid cells; there is no necrosis. There are no spermatozoa in the ducts. The *right testicle* is normal in every respect, spermatogenesis being very active.

B7: Death from tuberculosis itself. Tuberculosis 3+. The *left testicle* is a nodular, caseous mass, adherent in its sac at the caudad end. The iliac lymph nodes are enlarged and caseous. The tunica vaginalis of the *right testicle* is hyperemic and contains one or two tubercles.

Microscopic (see figures 6, 9 and 10): *Left testicle:* The tissue is almost entirely necrotic. There is some calcification, but very little fibrosis. A very few atrophied tubules remain near the tunica albuginea. Reticulin is present in considerable amount, but is much less dense than in A7, and in certain regions, which the hemotoxylin-eosin stain shows to be spots of necrosis, is almost absent. Little collagen is shown. The *left epididymis* is densely infiltrated with epithelioid cells. The tubules contain many polymorphonuclear leucocytes. In the *right testicle* there is marked hyperemia. There is a well-defined area of epithelioid cell infiltration, 1 to 2 mm. in diameter, near the junction of testicle and epididymis. Here the tubules are widely separated, atrophic and not producing spermatozoa. The *right epididymis* is normal.

A8 and B8 (51 days after testicle infection, 70 days after primary infection of A8)

A8: Gas. Tuberculosis 3+. The left testicle is small, not hard, not adherent in its sac, and slightly mottled with yellowish spots. The iliac lymph nodes are enlarged, especially the left.

Microscopic: Left testicle: About half of the tissue consists of tubules lined by a single layer of epithelium showing no spermatogenesis. The tubules are separated by young connective tissue and an increased number of interstitial cells of Leydig. The rest of the tissue consists of young connective tissue, scattered, much atrophied tubules, and numerous nodules of dense round cell infiltration, with epithelioid cells in the centre. There is no necrosis. The *epididymis* is normal, except for slight round cell infiltration and absence of spermatozoa from tubules. The *right testicle* is normal.

B8: Gas. Tuberculosis 3+ (much more extensive than in A8). The *left testicle* is enlarged and hyperemic and contains large spots of necrosis. The right and left iliac lymph nodes are enlarged and caseous. The epididymis is greatly swollen. The *right testicle* shows no gross change.

Microscopic: Left testicle: The parenchyma is almost completely replaced by a tissue consisting of epithelioid cells in which are numerous spots of caseation necrosis. There are a few areas of suppuration. A few tubules remain along the tunica. There is extensive suppuration in the *left epididymis*. *Right testicle:* There is a marked hydropic degeneration of the tubular epithelium. There is no spermatogenesis, the tubules containing a single basal layer of cells and no spermatocytes, spermatids or spermatozoa. There is a slight hyperplasia of the interstitial cells of Leydig. The *epididymis* is normal, except that the tubules contain no spermatozoa.

PROTOCOLS OF *C* AND *D* GUINEA PIGS

Reinfection in testicle compared with primary infection of testicle

Infections and death

	C guinea pigs	*D* guinea pigs
March 29, 1923	One-tenth of a milligram of R1 tubercle bacilli injected in left axilla	Noninfected
April 26, 1923	One one-hundredth of a milligram of H301 tubercle bacilli injected in left testicle	Same treatment as *C* guinea pigs
	Guinea pigs killed by illuminating gas at intervals or dead from intercurrent infection or from tuberculosis itself	Killed by gas with a *C* mate or dead from intercurrent infection or from tuberculosis itself

Necropsy findings

C1 and *D1* (*one day after testicle infection, 29 days after primary infection of C1*)

C1: Gas. Tuberculosis 1+ (see figure 1). The *left testicle* is much enlarged and extremely hyperemic. There is no definite necrosis, although some of the hyperemic tissue has a yellowish tinge. The *right testicle* is normal.

Microscopic: Left testicle: There is marked swelling of the tubules with profound degeneration of the germ cells and very extensive intertubular infiltration of wandering cells. The normal arrangement of cells within the tubules is destroyed. There is a definite loss of nuclear staining power in the spermatids. Polymorphonuclear cells are numerous in the interstitial tissue. The *right testicle* is normal.

D1: Gas. No tuberculosis except testicle infection (see figure 2). The *left testicle* is very slightly hyperemic but not enlarged. There are no abnormalities elsewhere.

Microscopic: Left testicle: There is a moderate infiltration of wandering cells, especially epithelioid and round cells, but no definite degeneration of the germ cells. On the whole it is not much changed from normal. The *right testicle* is normal.

C2 and *D2* (*4 days after testicle infection, 32 days after primary infection of C2*)

C2: Gas. Tuberculosis 1+. The *left testicle* is the same size as the right but decidedly hyperemic and shows necrosis in spots. The left iliac lymph nodes are enlarged. The *right testicle* is normal.

Microscopic: Left testicle: There is profound degeneration of the germ cells and very extensive intertubular wandering cell infiltration. There is definite coagulation necrosis of much of the tubular epithelium and infiltration of the necrotic tissue by wandering cells. Tubular outlines are indistinct. The *right testicle* is normal.

D2: Gas. No tuberculosis except that of testicle. The *left testicle* is the same size as the right, but hyperemic. There is no necrosis. The iliac lymph nodes are normal. The *right testicle* is normal.

Microscopic: Left testicle: The reaction is similar to that in D1 and only slightly more advanced. The *right testicle* is normal.

C3 and *D3* (*7 days after testicle infection, and 35 days after primary infection of C3*)

C3: Gas. Tuberculosis 1+. The *left testicle* is deeply injected with blood and there are large spots of necrosis up to 6 mm. in diameter in the lower pole. The left, but not the right, iliac lymph nodes, are slightly enlarged. The *right testicle* is normal.

Microscopic: Left testicle: There is almost complete coagulation necrosis of the tubular cells, the tubules consisting of large islands of swollen pink-staining cells, with no nuclear stain. There is marked wandering cell infiltration, and also an eosin staining fibrillar material (reticulin, fibrin?) between the tubules. The *right testicle* is normal.

D3: Gas. No tuberculosis except that of the testicle. The *left testicle* is somewhat enlarged and very hyperemic, but no necrosis is apparent. The left iliac lymph nodes are slightly enlarged. The *right testicle* is normal.

Microscopic: Left testicle: There is a dense epithelioid cell infiltration, replacing many of the tubules. The spermatocytes in the remaining tubules show various stages of degeneration up to complete chromatolysis. Spermatozoa are no longer seen. The *right testicle* is normal.

C4 and *D4* (*21 days after testicle infection, and 49 days after primary infection of C4*)

C4: Gas. Tuberculosis 2+. The *left testicle* is much enlarged, hard, discolored by hemorrhage, and adherent in its sac. The *epididymis* is also much enlarged. The left iliac lymph nodes are enlarged but not caseous. The *right testicle* is normal.

Microscopic: Left testicle: Similar to C3; many swollen, entirely necrotic tubules persist. There is intense wandering cell infiltration of the epididymis. The *right testicle* is normal.

D4: Intercurrent infection. Tuberculosis 2+. The *left testicle* is enlarged, hard, nodular and discolored with yellow spots of necrosis. One left iliac lymph node is enlarged and partly caseous. The *right testicle* shows no gross abnormalities.

Microscopic: Left testicle: There is extensive caseation necrosis and moderately extensive infiltration of wandering cells, chiefly of the epithelioid type. Only a few tubules remain and these are greatly atrophied. No tubules with marked coagulation necrosis, comparable to those seen in C4, are present. *Right testicle:* There is a marked hydropic degeneration of the tubular epithelium, and no spermatogenesis. There is some intratubular phagocytosis of germ cells. (The picture does not resemble a tuberculin reaction, and may be a sequel of the peritonitis from which the animal died.)

C5 and D5 (*33 days after testicle infection, 61 days after the primary infection of C5*)

C5: Gas. Tuberculosis 2+. The *left testicle* and epididymis are enlarged and hard. The testicle is adherent in its sac. The *right testicle* is normal.

Microscopic: Left testicle: Similar to C3 and C4. Islands of necrotic tubules persist, the tubules being perfect in outline, made up of cells taking the eosin stain only. The interstitial

tissue is infiltrated with epithelioid cells and some polymorphonuclear leucocytes. There is no definite fibrosis. There is a marked chronic periorchitis. The epididymis is infiltrated with epithelioid cells. The *right testicle* is normal.

D5: Gas. Tuberculosis 3+. The *left testicle* is enlarged, somewhat nodular and not adherent in its sac. It appears as sclerotic tissue containing a number of caseous nodules. The iliac lymph nodes, especially on the left side, are enlarged and partly caseous. The *right testicle* appears decreased in size.

Microscopic: Left testicle: There is a pronounced epithelioid cell reaction and very little necrosis. A few well defined epithelioid tubercles with necrotic centres are present. There is a definite early fibrosis. (*Note:* this is the one case in which a high degree of local resistance to a primary infection was encountered.) *Right testicle:* There is marked atrophy of the tubules and hyperplasia of the interstitial cells of Leydig. There is very little spermatogenesis. The picture resembles the one-month tuberculin reaction described below (*F2*).

D5a (44 days after testicle infection. No C mate was killed.)

D5a: Intercurrent infection. Tuberculosis 3+. The *left testicle* and epididymis together are slightly enlarged and nodular and adherent in the sac. The iliac lymph nodes are enlarged and caseous. The *right testicle* is decreased in size.

Microscopic: Left testicle: There is much caseation necrosis, with only a moderate epithelioid cell reaction. The testis is smaller than the epididymis. The tubules of the epididymis are full of pus, and there is much epithelioid cell proliferation between them. *Right testicle:* there is marked atrophy of the tubules. The appearance is that of a late tuberculin reaction (see F2). The epididymis is infiltrated with epithelioid cells and partly necrotic.

C6 and D6 (47 days after testicle infection, 75 days after primary infection of C6)

C6: Gas. Tuberculosis 2+. The *left testicle* is enlarged, hard, and adherent in its sac. The iliac lymph nodes are slightly enlarged but not caseous. The *right testicle* is normal.

Microscopic: Left testicle: There is a pronounced epithelioid cell reaction with much definite fibrosis, which gives a lobulated appearance to the testicle. A few small spots of necrosis occur. There is some localized edema. Polymorphonuclear leucocytes are numerous near the epididymis. The *epididymis* is profoundly changed. There is a marked epithelioid cell infiltration, much fibrosis and a great deal of suppuration within the tubules. The *right testicle* is normal.

D6: Gas. Tuberculosis 3+. The *left testicle* is small, hard and nodular, and adherent in its sac. The iliac lymph nodes are enlarged and caseous. The *right testicle* is decreased in size.

Microscopic: Left testicle: The body is completely necrotic. There is only a moderate epithelioid cell reaction, and there is much karyorrhexis and necrosis of the epithelioid cells. There is considerable chronic periorchitis. The *left epididymis* is infiltrated with epithelioid cells, but there is no necrosis. *Right testicle:* There is marked atrophy of the tubules with hyperplasia of the interstitial cells of Leydig. The reaction is a typical tuberculin one of the F2 type (see below). In the middle of the body of the testicle is a well-defined epithelioid tubercle with a necrotic centre; a few smaller, less well defined tubercles are near it. The *right epididymis* is normal, except that very few spermatozoa are present in the tubules.

C6a (77 days after testicle infection, 105 days after primary infection. No D mate.)

C6a: Gas. Tuberculosis 3+. The *left testicle* and epididymis together are four times normal size, mottled with yellow spots and adherent in the scrotal sac. The iliac lymph nodes, especially the left, are enlarged and contain small caseous spots. The *right testicle* appears normal.

Microscopic: Left testicle: Similar to C6, but the fibrosis and lobulation are more pronounced. The epididymis is also similar, but suppuration is advanced. The epididymis is four times the size of the testis. *Right testicle:* Spermatogenesis is not at all active; spermatocytes and spermatids are almost absent. There is no interstitial cellular infiltration or other sign of tuberculosis.

C6b (127 days after testicle infection, 155 days after primary infection. No D mate.)

C6b: Death from tuberculosis itself. Tuberculosis 3+. The *left testicle* and epididymis together are greatly enlarged and to some extent necrotic. The iliac lymph nodes, especially the left, are enlarged and caseous. The *right testicle* appears normal. No sections.

PROTOCOLS OF *E* GUINEA PIGS

Single testicle infection with tubercle bacilli of low virulence

Infection and death

March 13, 1923. One-tenth of a milligram of R1 tubercle bacilli inoculated into left testicle.

Guinea pigs killed by gas at varying intervals.

Necropsy findings

E1 (2 days after testicle infection)

E1: Gas. No tuberculosis except that of testicle. The *left testicle* is somewhat hyperemic. The *right testicle* is normal.

Microscopic: Left testicle: There is little change from normal. Spermatocytes and spermatids are formed in normal amount, but there is some diminution in the number of spermatozoa. There is a slight interstitial infiltration of wandering cells. The *right testicle* is normal.

E2 (9 days after testicle infection)

E2: Gas. No tuberculosis except that of testicle. The *left testicle* is hyperemic and contains a superficial area of necrosis. The *right testicle* is normal.

Microscopic: Left testicle: There is a patchy interstitial infiltration of round and epithelioid cells. There appears to be some hyperplasia also of the interstitial cells of Leydig (these are often difficult to distinguish from epithelioid cells, but in this case occur in large groups between tubules, where there is no definite inflammatory reaction). There is some slight necrosis; in these areas polymorphonuclear leucocytes are numerous. Spermatogenesis occurs, but is not active. The primary divisions occur, but spermatozoa are not numerous. The *right testicle* is normal and spermatogenesis is active.

E3 (16 days after testicle infection)

E3: Intercurrent infection. No tuberculosis except that of testicle. The *left testicle* is decreased in size and hyperemic; it is not adherent in its sac. A white nodule is apparent in the tunica. The *right testicle* is normal.

Microscopic: Left testicle: There is extensive infiltration of about one-half of the body of the testicle with epithelioid and round cells. Only a few tubules remain in this region; these are lined by a single layer of swollen cuboidal epithelium and show no spermatogenesis. There are no areas of necrotic tissue. No well defined tubercles and no giant cells are seen. In the other half of the testicle the tubules appear to be normal, showing active spermatogenesis. The *right testicle* is normal.

E4 (30 days after testicle infection)

E4: Gas. Tuberculosis 1+. The *left testicle* is decreased in size and hyperemic. There are numerous yellowish-white areas in the tunica. The iliac lymph nodes are somewhat enlarged, but not caseous. The *right testicle* is normal.

Microscopic: Left testicle: There is a moderate diffuse infiltration of epithelioid and round cells between the tubules throughout the body of the testicle. There is a marked hydropic degeneration of the tubular epithelium. The epididymis is normal, except that spermatozoa are absent from the tubules. The *right testicle* is normal.

SUMMARY OF PROTOCOLS ON GUINEA PIGS *A*, *B*, *C*, *D*, AND *E*: INFECTION AND REINFECTION

It will be seen at once that there is a profound difference in the response of the testicle to tubercle-bacillus infection in normal animals and animals already infected. The guinea pigs carrying a light intraperitoneal or axillary infection respond in twenty-four hours with marked hyperemia and swelling of the testicle. Microscopically, extraordinary degeneration or coagulation necrosis of the germ cells, interstitial and intracellular edema, and an intense epithelioid and wandering cell infiltration are observed. At this period, and for another twenty-four hours, the testicle of the guinea pig with no other tuberculosis shows practically no gross abnormalities, and microscopically only a moderate wandering cell infiltration.

After a time, as was pointed out by Soper, the tuberculosis of the guinea pigs not previously infected tends to catch up with that of the previously infected animals. From one to four weeks after the testicular infection the two groups may show no great differences. There is, however, a rather general tendency on the part of the previously infected guinea pigs to supplement the epithelioid reaction with the proliferation of fibroblasts and to limit the infection to the testicle, and a tendency on the part of the guinea pigs never before infected to suffer caseation necrosis of the infected testicle and marked extension to other organs. These results may be obscured by suppuration, which may intervene in either group. Whether this is due to secondary infection or the tubercle bacillus itself is as yet undetermined. A noticeable feature in the reinfected guinea pigs, which distinguishes the microscopic picture, is the slow absorption of the tubules which have undergone coagulation necrosis.

After six weeks there is usually a well-defined difference. The testicle of the previously infected animal is small, rich in epithelioid cells

and moderately rich in fibroblasts. There is little necrosis. Corresponding to the abundant proliferation of epithelioid cells there is a marked deposition of reticulin. This extraordinary fixed-tissue cell proliferation which follows reinfection in the sensitized animal has been frequently described by Krause and repeatedly emphasized by him for its bearing upon the phenomenon of resistance. A summary of the principles deduced by Krause and his co-workers from their experience in this connection is given by Krause and Peters in their article on *Local Allergic and Immune Reactions to Tuberculous Reinfection in Guinea Pigs* (AMERICAN REVIEW OF TUBERCULOSIS, 1920, iv, 551).

The subject of reticulin in chronic tuberculosis has been recently ably handled by William Snow Miller (8), whose coöperation has been of great assistance in the prosecution of the present work. In the other group, where the testicle infection was primary, the testicle is again small, but soft and largely necrotic. Microscopically, only a moderate epithelioid cell reaction is seen, and fibroblast proliferation is slight. Reticulin deposition is irregular and not dense. In either group the epididymis is likely to be much enlarged; and, whether because of its nearer association with the outside world, or some cause inherent in itself, it is prone to suppuration.

A very important distinction between the two is in the condition of the other testicle. In the reinfected animals degeneration of the right testicle was seen only once (A6). This was a case in which there was suppuration in the left testicle. In the group with primary virulent infection of the left testicle degeneration or actual tuberculosis of the right testicle was invariably seen late in the disease (B5, B6, B7, B8, D4, D5, D5a and D6). This was associated with more extensive generalization of the disease. The findings in D5a and D6 are especially worthy of comment. In D5a the right testicle appears to be infected by extension from the right epididymis, itself infected by extension from the left epididymis. In D6 the right testicle appears to be infected by the hematogenous route. In both cases the testicle has suffered what the experience of this investigation teaches is a typical tuberculin reaction. This late in the disease (4 to 6 weeks) the right testicle is of course sensitized soil.

Primary infection of the testicle with a tubercle bacillus of low virulence (*E* guinea pigs) is noteworthy for the slow progression of the disease. Extensive degeneration of the germinal epithelium is apparent only after three to four weeks, at a time when it is reasonable to suppose

that all tissues of the body are sensitized. At this period the highly susceptible germ cells of one part of the testicle could hardly be expected to escape contact with tuberculin from infected testicle tissue in close proximity. It is notable that this late in the course of the disease (4 weeks) the actual infective process has not overrun the entire body of the testicle and generalization has not begun. This finding naturally leads one to wonder if the course of the disease might not be still further obstructed by previous immunization of the animal with a small subcutaneous dose of the same slightly virulent microörganism. It seems as if such a procedure might fulfil the requirements of a slowly progressive, standard lession for experimental therapy.

PLAN OF EXPERIMENTS ON TUBERCULIN

Two guinea pigs were infected with a tubercle bacillus of low virulence (R1) and twenty-six days later given an intratesticular injection of 0.01 cc. O. T. After two days one of these was killed (F1); the other (F2) was killed one month later. Simultaneously with the tuberculin injection of F1 and F2, two normal male guinea pigs were similarly injected and allowed to live two days and one month respectively (G1 and G2). Another guinea pig (H1), infected with the R1 tubercle bacillus, was given an intratesticular inoculation of a filtered broth, consisting essentially of a solution of histidine, ammonium chloride, glycerol and salts, in which the tubercle bacillus (H37) had been cultivated for two months. This tuberculin gave a very faint biuret test, possibly attributable to the histidine, and a few of the other so called protein tests. It was a good example of what is commonly called a nonprotein tuberculin, but possibly contained a minute trace of protein extracted from or excreted by the bacillus.

The tuberculin reaction in the testicle of two old male guinea pigs (I1 and I2) with a chronic, practically latent tuberculosis was also studied. These guinea pigs had been inoculated in the groin by Dr. De Witt two years and two months before my experiments, with a tubercle bacillus of rather low virulence (H1305), and at one time had had large inguinal lymph node lesions, but for many months had been increasing in weight in normal fashion and appeared to be healthy guinea pigs. It is noteworthy that their skin reaction to tuberculin was negative. The protocols for these guinea pigs (*F*, *G*, *H*, and *I* guinea pigs) follow.

PROTOCOLS FOR *F* AND *G* GUINEA PIGS

Action of tuberculin on the testicle of infected and noninfected guinea pigs

Inoculation and death

	F guinea pigs	*G* guinea pigs
March 29, 1923	One tenth of a milligram of R1 tubercle bacilli injected into left axilla	Noninfected
April 24, 1923	One one-hundredth of a milligram of Old Tuberculin injected in left testicle	Same treatment as *F* guinea pigs
	Guinea pigs killed by gas at end of two days and one month, or dead from intercurrent infection	Same as *F* guinea pigs

F1 and G1 (2 days after injection of tuberculin into testicle, 28 days after primary infection of F1)

F1: Gas. Tuberculosis 1+. The *left testicle* is much enlarged and extremely hyperemic. (The picture is identical with that seen in figure 1.) It is hard and shows no gross necrosis. The *right testicle* is normal.

Microscopic: Left testicle (figure 11): Every tubule is tremendously swollen. The individual cells are separated and themselves swollen. The swelling of the cytoplasm of the spermatocytes is especially noticeable, and the staining power is decreased. Apparently there is beginning necrosis. The normal arrangement of germ cells is distorted. Spermatozoa have disappeared from the tubules to some extent, and the lumina are filled with swollen spermatocytes, debris and precipitated protein. The spermatids show various stages of degeneration. The spermatogonia show less change. Mature spermatozoa seem normal. There is extensive intertubular edema, much infiltration of wandering cells including epithelioid cells, lymphocytes, eosinophiles, polymorphonuclear leucocytes and some cells of the plasma cell type. The interstitial cells are swollen. There is some interstitial edema of the epididymis. The *right testicle* is normal.

G1: Gas. No tuberculosis. The *left testicle* is not hyperemic or swollen. No abnormalities are seen, except a small hemorrhage in the tunica at the site of the tuberculin injection. The *right testicle* is normal.

Microscopic: Left testicle: Practically normal. There is a slight edema in the centre, but no infiltration of wandering cells. The *right testicle* is normal.

F2 and G2 (28 days after injection of tuberculin into testicle, 54 days after primary infection of F2)

F2: Gas. Tuberculosis 2+. The *left testicle* is half the size of the right, soft, flabby and very slightly hyperemic. There is no necrosis and the tunica, aside from the hyperemia, appears normal. The *right testicle* is normal.

Microscopic: Left testicle (figure 12): There is profound atrophy of the tubules. Every tubule is perfectly lined by a basement membrane, lying upon which is a single layer of cells with a large vesicular nucleus, slightly granular, with one small densely staining nucleolus. These are perhaps spermatogonia, or may be considered merely as undifferentiated epithelial cells. A mass of pink-staining fibrils extends toward the centre. This usually stops abruptly, leaving a well-defined lumen. No spermatocytes, spermatids or spermatozoa are present. There is a marked interstitial hyperplasia. The interstitial cells of Leydig are extraordinar-

ily increased in number, and numerous epithelioid cells are present. The *epididymis* is normal, except that only in the distal part of the tubules are any spermatozoa present. The *right testicle* is normal; spermatogenesis is very active. (Figure 13.)

G2: Intercurrent infection. No tuberculosis. The *left testicle* is the same size as the *right* and both appear normal.

Microscopic: The *left and right testicles* are similar and show no effects of tuberculin injection.

PROTOCOL OF *H* GUINEA PIG

Effect of tuberculin prepared from a nonprotein medium (consisting essentially of histidine, ammonium chloride, glycerol and salts) upon the testicle of a tuberculous guinea pig

May 18, 1923. One-tenth of a milligram of *R1* tubercle bacilli injected in left axilla.

June 19, 1923. One one-hundredth of a cubic centimetre of tuberculin from protein-free medium injected into left testis.

June 20, 1923. Guinea pig killed by gas.

H1 guinea pig (24 hours after injection of tuberculin into testicle, 33 days after primary infection in axilla)

H1: Gas. Tuberculosis 2+. The *left testicle* is at least 50 per cent enlarged and the tunica is extremely hyperemic. There is a slight exudate of fibrin on its surface. The *right testicle* is normal.

Microscopic: Left testicle (figure 14): The picture is somewhat less advanced, but otherwise closely similar to that seen in the left testicle in F1. Eosinophiles are especially conspicuous in the intertubular exudate. The *right testicle* is normal.

PROTOCOL OF *I* GUINEA PIGS

Effect of tuberculin upon the testicle of guinea pigs with latent tuberculosis of more than 2 years' duration

January 15, 1921. Guinea pigs infected in left groin with H1305 (by Dr. DeWitt), a tubercle bacillus of low virulence.

May 15, 1923. One one-hundredth of a cubic centimetre of Old Tuberculin injected in left testicle.

May 17, 1923. Guinea pigs killed by gas.

I1 (2 days after injection of tuberculin into left testicle, 2 years and 2 months after primary infection in groin)

I1: Gas. Tuberculosis 3+, but latent. The *left testicle* resembles the right. Both are normal. There is absolutely no reaction. The spleen is small, hard and nodular. The lungs and liver are coarsely nodular. Numerous lymph nodes are increased in size, hard and dense. Those of the groin are very sclerotic.

Microscopic: Left testicle: Normal, spermatogenesis active. *Right testicle:* Normal, spermatogenesis active. *Spleen:* There is a marked fibroplastic and epithelioid reaction. A few small areas of karyorrhexis are present. A few giant cells are seen. *Lungs:* There are numerous areas of dense epithelioid cell and fibroblast proliferation, with considerable collagen. There are a few spots of necrosis in these areas, sharply limited by fibrous tissue. There is a peribronchial and perivascular lymphoid hyperplasia.

I2 (duplicate of I1)

Gross and microscopic findings practically identical with I1.

SUMMARY AND DISCUSSION OF PROTOCOLS OF *F*, *G*, *H*, AND *I* GUINEA PIGS: TUBERCULIN

The outstanding fact brought out by the above protocols is the extraordinary susceptibility of the germ cells of guinea pigs suffering with active tuberculosis to tuberculin (see figure 11). It is not surprising that these cells should be more severely injured than a connective tissue cell or a lymphocyte or a liver cell. Degree of cell specialization and susceptibility to injury are directly proportional throughout pathology, and surely germ cells have a high degree of specialization. The spermatocyte and spermatid, that is, the primary and secondary stages of division, seem to be the vulnerable spots in the maturation process. Spermatogonia and spermatozoa seem less susceptible to injury. The immediate effect of tuberculin, apparent in twenty-four hours, is a marked hyperemia of both testicle and tunica, and swelling. Microscopically, there is intertubular edema, wandering cell infiltration, and degeneration and beginning necrosis of the spermatocytes and spermatids. The picture is like that seen in reinfection, but the reaction is less intense, perhaps because 0.01 to 0.1 mgm. tubercle bacilli represents a much higher dose of tuberculin than 0.01 cc. O. T. The tuberculin prepared from a non-protein medium is effective in the same manner as O. T.

At this period (twenty-four hours), when the testicle of the previously infected guinea pig is so highly inflamed, the testicle of the noninfected one shows little or no change either grossly or microscopically. Tuberculin, so destructive to the testicle of the infected guinea pig, is absolutely nontoxic for the testicle of the normal animal.

The picture one month after the tuberculin reaction (see figure 12) is fully as striking. The injured germ cells have no power of recovery. Spermatocytes, spermatids and spermatozoa have disappeared; the tubules remain lined by large cells, which are perhaps to be considered spermatogonia or possibly as Sertoli cells. Pictures that I have seen in the gland transplants of Dr. Carl Moore incline me to the former view. If they are spermatogonia, however, their power to initiate the maturation process seems permanently destroyed. While the germinal epithelium has undergone such extraordinary atrophy, the interstitial cells (of Leydig) have proliferated in a striking manner. The whole picture reminds one of the extreme effects of alcohol (9) or of the atrophy which may follow vasectomy or ligation of the ductus deferens (Steinach and similar operations). Complete sterilization has been effected. The

testicles of the noninfected animals show no changes; and in them, neither immediately nor in its after effects, has tuberculin proved injurious to the tubular epithelium.

The results obtained with the *I* series of guinea pigs (tuberculin injected into the testicle two years and two months after primary infection) show that animals which at one time were unquestionably highly hypersensitive have become tolerant to tuberculin. No reaction followed the injection of tuberculin into the testicle. This is, of course, in principle, no new finding. A fading of the cutaneous reaction to tuberculin, as the internal tuberculous lesion healed, has been frequently observed. The interesting point is that the lesions of the animals were not absolutely quiescent, and were certainly vastly more extensive than the early, small, but caseous, axillary gland lesions of the *D* guinea pigs, which conferred such exquisite hypersensitiveness upon all tissues. It is noteworthy, however, that extensive as were the lesions of the *I* series of guinea pigs they were of the fibroplastic type, with extremely little necrosis. So little tissue hypersensitiveness to tuberculin remains that even the easily injured germ cells do not react.

PLAN OF EXPERIMENTS WITH A NONPATHOGENIC ACID-FAST BACILLUS AND A NON-ACID-FAST BACILLUS (*J*, *K*, AND *L* GUINEA PIGS)

The experiments of Krause and Baldwin on cross sensitization and skin allergy in the group of acid-fast bacteria indicated quite clearly that tuberculous animals are hypersensitive to extracts of various nonpathogenic acid-fast bacilli, and conversely that guinea pigs "infected" with the nonpathogenic acid-fasts react to tuberculin in the same manner as tuberculous guinea pigs. This significant indication of a biological relationship between these types of bacilli, alike in their peculiar staining property, but so different in virulence, I have checked by the testicle method for tissue allergy herein described.

Two guinea pigs were infected with tubercle bacilli (H301) in the left axilla and twenty-six days later, at a time when the cutaneous response to tuberculin was very active, given intratesticular inoculations of 0.1 mgm. of acid-fast turtle bacilli and non-acid-fast paratyphoid bacilli, respectively. At the same time a normal, noninfected guinea pig was inoculated in the testicle with the same amount of turtle bacilli. Experiments of this character on a greater scale will be reported in future articles.

PROTOCOLS OF *J*, *K*, AND *L* GUINEA PIGS

Comparative effects of nonpathogenic, acid-fast bacilli, and pathogenic, non-acid-fast bacilli upon tuberculous guinea pigs

	J	*K*	*L*
April 26, 1923	One one-hundredth of a milligram of H301 (a highly virulent tubercle bacillus) injected in left axilla	Noninfected	Same as *J*
May 22, 1923	One-tenth of a milligram of turtle bacilli injected in left testicle	Same as *J*	One-tenth of a milligram of paratyphoid bacilli injected in left testicle
May 24, 1923	Killed by gas	Killed by gas	Killed by gas

Protocols of J, K, and L guinea pigs (2 days after testicle infection, 28 days after primary infection of J and L)

J: Gas. Tuberculosis 3+. The *left testicle* is slightly hyperemic and slightly enlarged. The picture is that of a mild tuberculin reaction. The *right testicle* is normal.

Microscopic: Left testicle: There is a definite degeneration of the germ cells, the spermatocytes and spermatids appearing swollen. There is a marked intertubular infiltration of wandering cells of all sorts, particularly epithelioid cells. The *right testicle* is normal.

K: Gas. No tuberculosis. The *left testicle* is slightly hyperemic, but not increased in size. The *right testicle* is normal.

Microscopic: Left testicle: Almost normal. There is a moderate infiltration of wandering cells, including many eosinopbiles. The *right testicle* is normal.

L: Gas. Tuberculosis 3+. The *left testicle* is slightly enlarged and slightly hyperemic. The *right testicle* is normal.

Microscopic: Left testicle: There is some traumatic distortion of structure. There is a slight swelling of the tubules but no definite degeneration of the germ cells. There is a moderate intertubular infiltration of polymorphonuclear leucocytes. The *right testicle* is normal.

SUMMARY ON PROTOCOLS ON *J*, *K*, AND *L* GUINEA PIGS: NONPATHOGENIC ACID-FAST AND PATHOGENIC NON-ACID-FAST BACILLI

A definite reaction has occurred in the testicle of the tuberculous guinea pig upon the introduction of turtle bacilli. The picture is that of a mild reaction to tuberculin. Inasmuch as the normal guinea pig did not give this type of reaction, we must conclude that the tuberculous guinea pig is specifically sensitive to something in the body of the turtle bacillus. Put in other words, the turtle bacillus contains tuberculin, whatever that is. The reaction to the paratyphoid bacillus is of entirely different character, expressed chiefly by an infiltration of polymorphonuclear leucocytes and slight edema. The germ cells are not

injured, as they would be were the tuberculous guinea pig hypersensitive to something within the paratyphoid bacillus. Turtle bacilli, and not paratyphoid bacilli, have in common with the tubercle bacillus something within their bodies to which the cells of the tuberculous animal are specifically sensitive. In our present day lack of a more definite chemical characterization we call this substance or these substances tuberculin. The testicle test herein described is as sensitive a test for its presence as the skin test, and fully as reliable. I should add that the generalizations of this paragraph are based partly upon work to be reported in the next article.

SUMMARY ON OTHER ORGANS THAN TESTICLES

The left spermatic vein was invariably dilated when there was inflammation of the left testicle. The marked hyperemia of the tunicae albuginea and vaginalis of the twenty-four-hour tuberculin reaction in the testicle was accompanied by a dilatation of the corresponding spermatic vein of 100 to 200 per cent. As a general principle, it can be stated that whenever the testicle is the seat of a tuberculin reaction, the spermatic vein will be much larger than that draining the normal testicle.

In all, forty sections of kidneys from twenty-four tuberculous guinea pigs were examined. In not a single instance was a well defined tubercle found. Special care was given to this feature of the investigation, because in the guinea pigs examined by Maver and Wells, in which Dr. DeWitt had made direct testicular inoculation, spots resembling tubercles were occasionally found in the kidneys. The possibility of an ascending infection was considered. In my series, in four animals out of twenty-four examined, kidney changes possibly, though not certainly, attributable to the tuberculosis were found. This incidence apparently bore no relation to the type of tuberculosis of the guinea pig. The changes referred to were small areas of slight epithelioid hyperplasia, by no means dense, and round cell infiltration around some glomeruli and the vessels leading to and from them. Occasionally an albuminuria was localized to such areas. Once a kidney was seen in which the tubules were slightly swollen and a considerable amount of protein was present in the lumen, a picture resembling the nephrosis in terminal tuberculosis sometimes seen in man. It was early learned that in looking for epithelioid cell hyperplasia one must be on guard against areas of collapsed or undeveloped tubules, otherwise normal.

As a routine procedure the prostate, seminal vesicles, ejaculatory ducts, ureters, urinary bladder and rectum were removed together, and a single section showing all was cut. Only one abnormality was ever encountered. Whenever tuberculosis was advanced in one testicle and had been so for some time, or the testicle was the seat of an atrophy of some duration, the corresponding ejaculatory duct, in contrast to its mate, was free from spermatozoa.

Liver, spleen and lung sections revealed nothing of new interest.

GENERALIZATIONS ON THE MORPHOLOGY OF THE TUBERCULIN REACTION WITH PARTICULAR REFERENCE TO THE RESPONSE OF THE HYPERSENSITIVE TESTICLE TO TUBERCULIN

The hypersensitiveness of infection is a composite matter, consisting of the sum total of the hypersensitiveness of various cells. Infection of one part of the body with tuberculosis confers a peculiar sensitivity upon most if not all body cells, of such character that when tuberculin is brought into contact with these cells the metabolism of the cells is profoundly altered, and the conspicuous manifestations of the tuberculin reaction develop, namely, vasodilation, edema, necrosis and wandering cell infiltration. These manifestations will now be considered separately.

In recent years much light has been thrown upon the subject of capillary tone and its alterations. Krogh has shown that many capillaries are ordinarily empty, and capillary innervation, heretofore unsuspected, has come to be an accepted fact in physiology. The nervous influence in turn can be modified or temporarily set aside by a great variety of substances, ranging in activity from the powerful capillary poison histamine to such weak acids as carbon dioxide. It has been concisely said that "the nervous control may be looked upon as a force tending to restrict the capillary beds over the body as a whole, maintaining a tone to be played upon by chemical factors." Ordinarily, in all probability, dilatation of the capillaries occurs under the influence of chemical factors in such a way that the wants of local tissue are supplied. To cite a simple example: in asphyxia dilatation may occur and permit ingress of an increased oxygen supply to the part.

A great variety of irritants are capable of setting up pathological dilatation. Some such irritant is concerned in the tuberculin reaction, formed on contact between tuberculin and sensitized soil. We are

more profoundly ignorant of the nature of this irritant than of tuberculin itself; nor are we sure of the precise site of its formation, although there is much reason for believing that it is formed within the sensitized cells themselves, including the endothelial cells of the capillaries, in the event of the tuberculin reaction. But, whether formed in the sensitized endothelium or in the fluid bathing it, the effect upon the vessel is a loss of capillary tone, and the part is flushed with blood until the effect wears off.

The explanation of the edema is more difficult. We are still in the dark concerning the mechanism by which edema occurs, although the rôle of the physicochemical factors, acid hydration of colloids and increased osmotic pressure from retention of crystalloids, is of unquestioned importance. Asphyxia favors both of these effects, and it may well be that in the tuberculin reaction the substance responsible for the vasodilation, referred to above, profoundly affects the oxidative capacity of the cells. The asphyxiated tissues will then hold more than the normal amount of water, interstitial partly, but intracellular especially, because by virtue of their peculiar hypersensitivity to tuberculin the cells will contain the injurious substance in concentrated form. The first hydration will be of these degenerating cells.

But the response of the sensitized cell to tuberculin may not be limited to edema, any more than it is confined to particular cells. The fate of the spermatocytes and spermatids, noted above, indicates possible later effects. These extraordinarily sensitive cells, hypersensitive to tuberculin, on contact with tuberculin became first swollen, then necrotic, and finally absorbed. Doubtless no new element, different from that discussed in the preceding paragraph, was introduced to cause the necrosis. Cells poisoned to the point of asphyxia may be excessively poisoned to death. Whether or not they will be replaced by new cells of the same sort, or by less specialized tissue, or not at all, depends upon the native character of the particular tissue.

But, again, the tuberculin reaction has its active as well as passive elements. Proliferation accompanies and succeeds degeneration. Wandering cell infiltration is not all, or even chiefly, due to capillary leakage. Specific chemotaxis plays a very important rôle. The epithelioid cell, again using this term as synonomous with the many terms employed to designate the well known large mononuclear phagocyte, in the tuberculous animal is a sensitized cell. It responds to tuberculin in a manner different from that of the corresponding cell of the nontuberculous

animal. Its metabolism too is affected and it becomes swollen. But it is a hardy individual, infinitely more rugged than the delicate spermatocyte, and proliferates where the other one dies. More than that, it is apparently specifically drawn to the site of the tuberculin, perhaps by the surface tension modification of the swollen cell.

If the reaction which we have been considering is a reaction to tuberculin pure and simple, and not infection, it will subside with the disappearance or destruction of the tuberculin. A return to normal may result, with tissue repair, if the damage was great, or atrophy, if the tissue was highly specialized. We have seen what happens to the highly specialized male gonad, and we are familiar with the return to normality on the other hand in the far less specialized skin. If, however, infection with the living organism supplements the tuberculin reaction there is a foreign body producing tuberculin and at the same time sensitizing tissue to it. The resultant picture is naturally very complex.

SUMMARY

1. Guinea pigs already infected with tuberculosis respond to tubercle-bacillus infection of the testicle within twenty-four hours with marked hyperemia and swelling of the organ, interstitial edema, intracellular edema and beginning necrosis of the spermatocytes and spermatids, and an intense wandering cell infiltration in which epithelioid and round cells are conspicuous. Infection of the testicle of the nontuberculous guinea pig leads, within twenty-four hours, to very slight changes.

2. In the previously infected animal coagulation necrosis of the tubular germinal epithelium follows the primary swelling, and absorption of necrotic tissue and steady increase in epithelioid cells go on together. In the animal previously not infected epithelioid cell infiltration soon becomes intense, with extensive absorption of testicle tubules, which however do not go through the stage of coagulation necrosis noted in the already tuberculous animal. After three to four weeks the lesions may look alike, except that there is a tendency to more marked epithelioid cell proliferation and to the growth of fibroblasts on the part of the testicle of the sensitized animal, while in the testicle of the nonsensitized animal there is a less marked epithelioid reaction and a definite tendency to caseation necrosis.

3. Unless the results are modified by suppuration, which may intervene in either group, the testicle of the immunized animal is apt, after

six weeks, to be densely infiltrated with epithelioid cells and moderately fibrous, with little necrosis, while that of its nonimmunized mate may be largely necrotic, with a much less extensive epithelioid cell and fibroblast reaction. Corresponding to the greater density of epithelioid cells there is a coarser deposition of reticulin in the testicle of the immunized animal. In neither case is there the slightest spermatogenesis, nor do many tubules remain recognizable.

4. Generalization is earlier and more extensive in the nonimmunized animal. Infection of the opposite testicle, hematogenous or by extension, is likely to occur late in the nonimmunized guinea pig. It has not been observed in the immunized. When it does occur, a tuberculin reaction, like that described below, occurs, with destruction of the germinal elements, the animal having become hypersensitive.

5. With a tubercle bacillus of low virulence a primary tuberculosis of the testicle may be produced, which is slowly progressive and remains restricted to the testicle for weeks.

6. When tuberculin is introduced in a small dose into the testicle of a tuberculous guinea pig, a prompt reaction occurs, with marked hyperemia and swelling, and a progressive degeneration of the germ cells, beginning with intracellular edema, extending to hydropic degeneration and necrosis, and ending after four weeks with complete absorption of all but an undifferentiated lining epithelium. Accompanying the atrophy of the germ cells is an epithelioid cell infiltration of the interstitial tissue and an extraordinary proliferation of the interstitial cells of Leydig. Sterilization of the testicle is complete. The opposite testicle is not affected. Tuberculin in a small dose has no effect, either early or late, upon the testicle of a nontuberculous guinea pig.

7. In eliciting the type of reaction just described, tuberculin prepared from a nonprotein medium, consisting essentially of histidine, ammonium chloride, glycerol and salts, is effective in the same manner as Old Tuberculin.

8. Guinea pigs with old extensive, but latent, nonprogressive tuberculosis may fail altogether to exhibit a tuberculin reaction of the testicle, just as they may fail to respond to the cutaneous test. In this investigation two guinea pigs, infected two years and two months previously, received tuberculin in the testicle without injury, in a dose which certainly would have caused profound degeneration of the germ cells in guinea pigs with fresh active tuberculosis.

9. When turtle bacilli are introduced into the testicle of a tuberculous guinea pig, what may be interpreted, on the basis of the findings described in paragraph 6 of this summary, as a tuberculin reaction occurs. A similar reaction does not result from the injection of turtle bacilli into the testicle of a normal animal nor from the injection of paratyphoid bacilli into a tuberculous animal. This indicates that the nonpathogenic acid-fast turtle bacillus contains some of the highly specific product of the tubercle bacillus, tuberculin.

10. In forty sections of kidneys from twenty-four tuberculous guinea pigs a definite tubercle has not been seen. In four of these, slight epithelioid cell and round cell hyperplasias, localized but not dense, with slight associated albuminuria, may possibly be attributable to tuberculosis.

11. In sections routinely made from tuberculous guinea pigs, in which the urinary bladder, prostate, seminal vesicles, ejaculatory ducts, ureters and rectum were included in one section, no abnormality was encountered except the absence of spermatozoa from that ejaculatory duct leading from an infected or atrophied testicle.

12. Generalizations on the morphology of the tuberculin reaction, drawn from observation of the testicle reaction, are made in the paragraphs preceding this summary.

I am indebted to Mr. George Zollars for much technical assistance and to Mr. José K. Santos for the drawing of colored figures 1 and 2.

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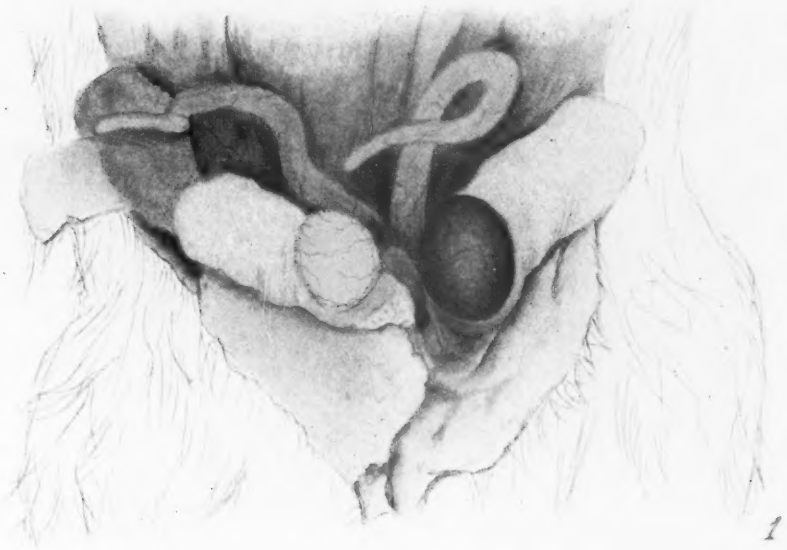
FIGURES

FIG. 1. REINFECTION (AFTER 24 HOURS)

Guinea pig C1. Inoculated in left axilla with 0.1 mgm. tubercle bacilli of low virulence (R1), March 29, 1923, and in left testicle with 0.01 mgm. highly virulent tubercle bacilli (H301), April 26, 1923. Killed 24 hours later. Abdominal cavity opened. Testicles pulled out of scrotal sac. Note great increase in size of left testicle and marked hyperemia. The reaction is a typical tuberculin reaction. A reaction of equal intensity is invariably given on injection of any form of soluble tuberculin comparable in amount to 0.01 cc. O. T.

FIG. 2. FIRST INFECTION (AFTER 24 HOURS)

Guinea pig D1. Inoculated in left testicle with 0.01 mgm. highly virulent tubercle bacilli, April 26, 1923. Killed 24 hours later. Abdominal cavity opened. Testicles pulled out of scrotal sac. Compare with figure 1 and note absence of reaction. Soluble tuberculin is equally ineffective in causing a testicle reaction in a noninfected guinea pig.



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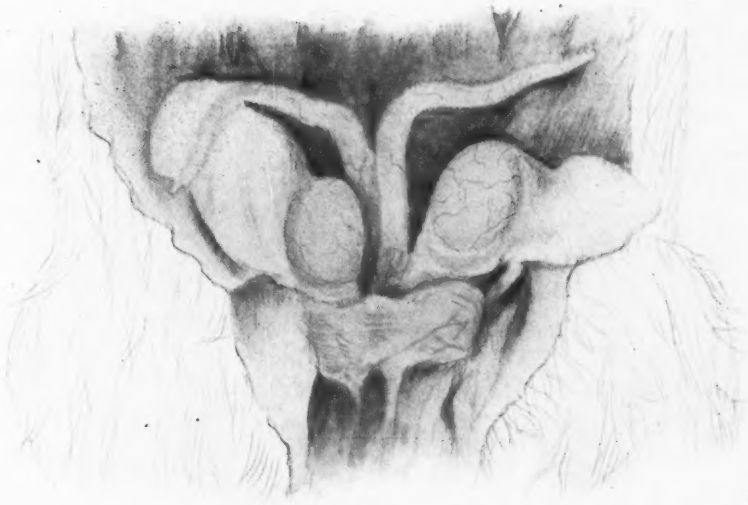

2

FIG. 3. REINFECTION (AFTER 48 HOURS)

Section of left testicle of guinea pig A1 (×70). First infection intraperitoneal, with 0.1 mgm. tubercle bacilli of low virulence (R1), February 1, 1923. Second infection intratesticular with 0.1 mgm. tubercle bacilli of moderately high virulence (H37), March 13, 1923. Guinea pig killed 48 hours later. Note profound degeneration of germinal cells and marked intertubular infiltration of wandering cells. This is essentially a marked tuberculin reaction plus a foreign body reaction.

FIG. 4. FIRST INFECTION (AFTER 48 HOURS)

Section of left testicle of guinea pig B1. (×70). Infection with 0.1 mgm. tubercle bacilli of moderately high virulence (H37), March 13, 1923. Guinea pig killed 48 hours later. Compare with figure 3. Note practical absence of any reaction. There is a slight intertubular infiltration of wandering cells, and most of the mature spermatozoa normally present in the lumina of the tubules have been discharged.

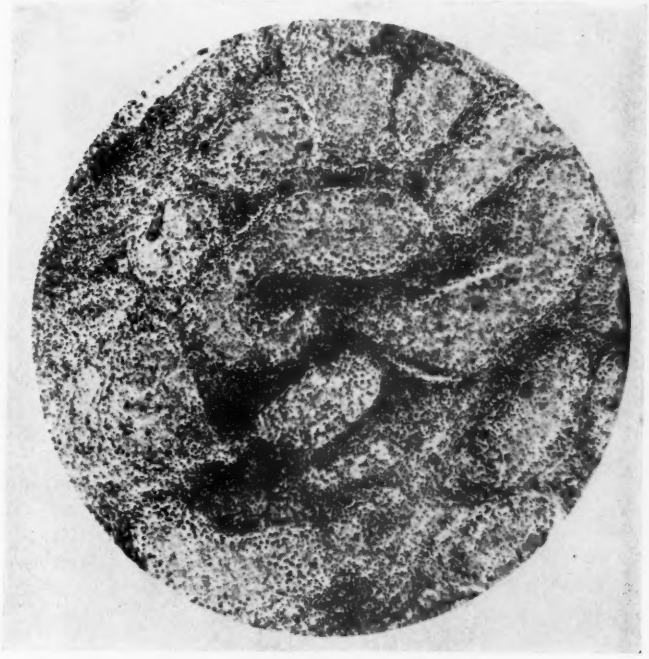

FIG. 3

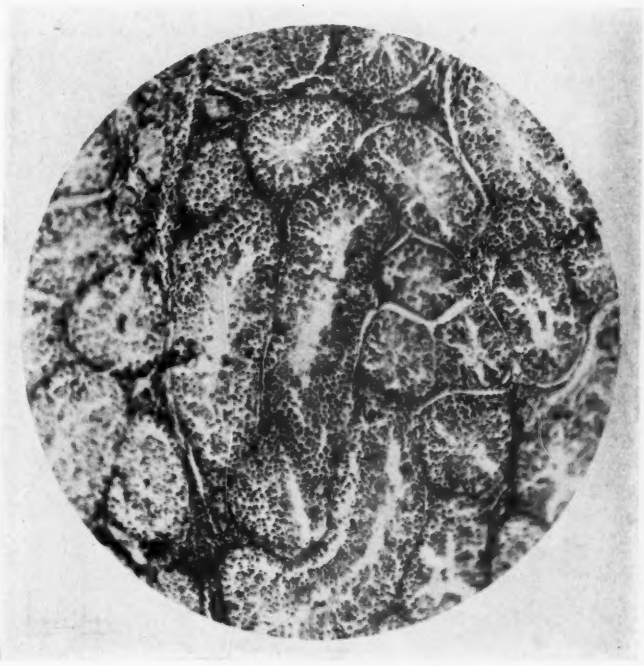

FIG. 4

FIG. 5. REINFECTION (AFTER 37 DAYS)

Section of left testicle of guinea pig A7 (×70). First infection intraperitoneal with 0.1 mgm. tubercle bacilli of low virulence (R1), February 1, 1923. Second infection intratesticular with 0.1 mgm. of tubercle bacilli of moderately high virulence (H37), February 20, 1923. Guinea pig killed March 29, 1923. Note almost complete destruction of tubules, marked epithelioid cell reaction, and definite growth of fibrous tissue. The reaction indicates good resistance to the infection.

FIG. 6. FIRST INFECTION (AFTER 37 DAYS)

Section of left testicle of guinea pig B7 (×70). Infection with 0.1 mgm. tubercle bacilli of moderately high virulence (H37), February 20, 1923. Guinea pig killed March 29, 1923. Compare with figure 5. Note complete destruction of tubules, moderate epithelioid cell reaction, karyorrhexis and necrosis, and absence of fibrous tissue. The reaction indicates poor resistance to the infection.

FIG. 5

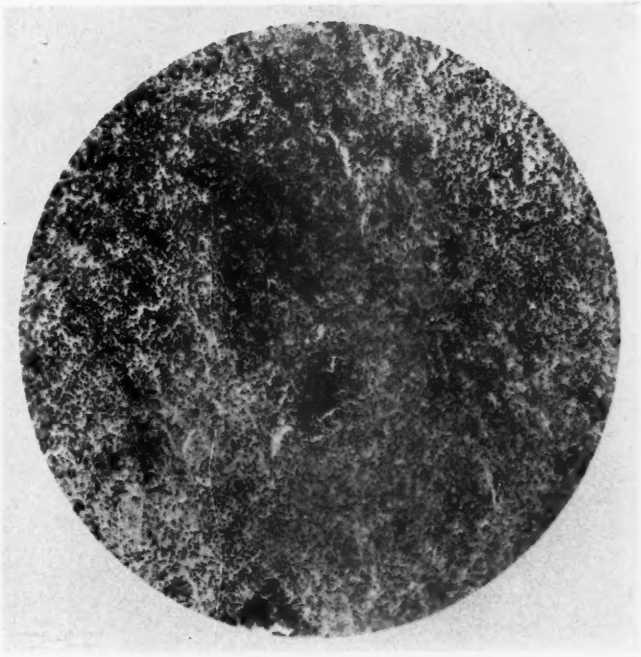

FIG. 6

FIG. 7. REINFECTION (AFTER 37 DAYS)

Section of left testicle of guinea pig A7 (×170). High power of same testicle as figure 5. (Hematoxylin and eosin preparation by Dr. William Snow Miller.) Note persistence of a few tubules lined by undifferentiated cells lying upon intact basement membrane. Note marked epithelioid cell, round cell and fibroblast infiltration.

FIG. 8. REINFECTION (AFTER 37 DAYS)

Section of left testicle of guinea pig A7 (×170). Reticulin stain (preparation by Dr. William Snow Miller) corresponding exactly to figure 7. Note coarseness of reticulin. The dense network in the upper right quadrant is the intercellular material of white fibrous tissue. The black mass lying chiefly in the lower left quadrant appears to be made up of the cytoplasm of epithelioid cells.

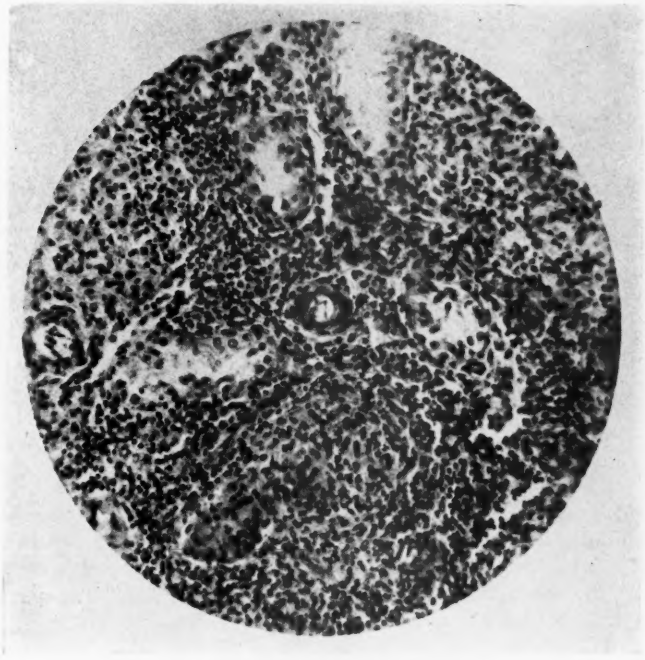

FIG 7

FIG. 8

FIG. 9. FIRST INFECTION (AFTER 37 DAYS)

Section of left testicle of guinea pig B7 (×170). High power of same testicle as figure 6. (Hemotoxylin and eosin preparation by Dr. William Snow Miller.) Note absence of tubules and necrosis in upper left quadrant. The epithelioid cell infiltration is less dense than in A7 (figure 7). The structure extending from "2 o'clock" to "6 o'clock" is an open tissue space conducting lymph, but not a true endothelium-lined lymphatic.

FIG. 10. FIRST INFECTION (AFTER 37 DAYS)

Section of left testicle of guinea pig B7 (×170). Reticulin stain (preparation by Dr. William Snow Miller) corresponding exactly to figure 9. Compare with figure 8. Note that considerable reticulin is present, but that it is not as dense as in A7 (figure 8). It is almost absent from the area of necrosis in the upper left quadrant.

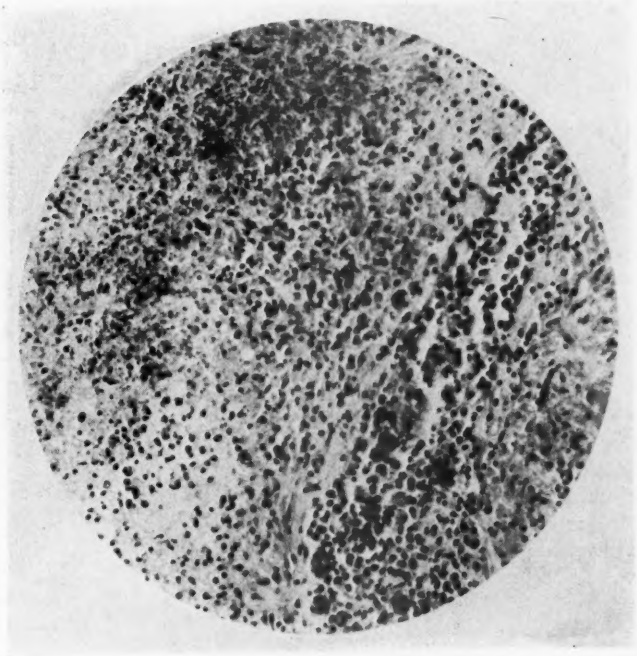

FIG. 9

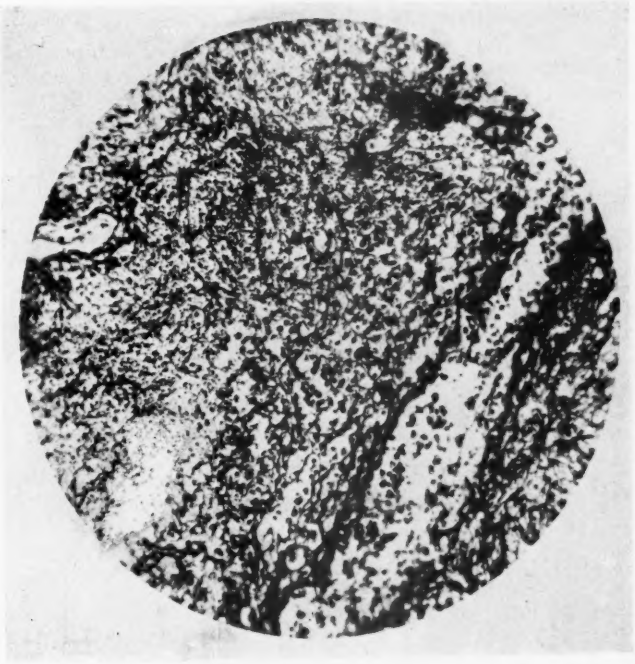

FIG. 10

FIG. 11. TUBERCULIN REACTION (AFTER 48 HOURS)

Section of left testicle of guinea pig F1 (×70). Infected in left axilla with 0.1 mgm. tubercle bacilli of low virulence (R1), March 29, 1923; 0.01 cc. O. T. injected in left testicle, April 24, 1923. Guinea pig killed 48 hours later. Gross picture at necropsy similar to figure 1. Note great swelling of tubules (compare with figure 13, which shows a normal testicle) and intertubular infiltration of wandering cells and some edema. The germinal cells are necrobiotic. Had this guinea pig been allowed to live one month the left testicle would presumably have appeared as in figure 12.

FIG. 12. TUBERCULIN REACTION (AFTER 4 WEEKS)

Section of left testicle of guinea pig F2 (×70). Infected in left axilla with 0.1 mgm. tubercle bacilli of low virulence (R1), March 29, 1923; 0.01 cc. O. T. injected in left testicle, April 24, 1923. Guinea pig killed May 22, 1923. Left testicle much reduced in size. Presumably two days after tuberculin injection this testicle had the appearance seen in figure 1 and microscopically in figure 11. Note extraordinary atrophy of tubules, with practically complete destruction of germinal elements. Note also extensive infiltration of epithelioid cells and marked proliferation of interstitial cells of Leydig.

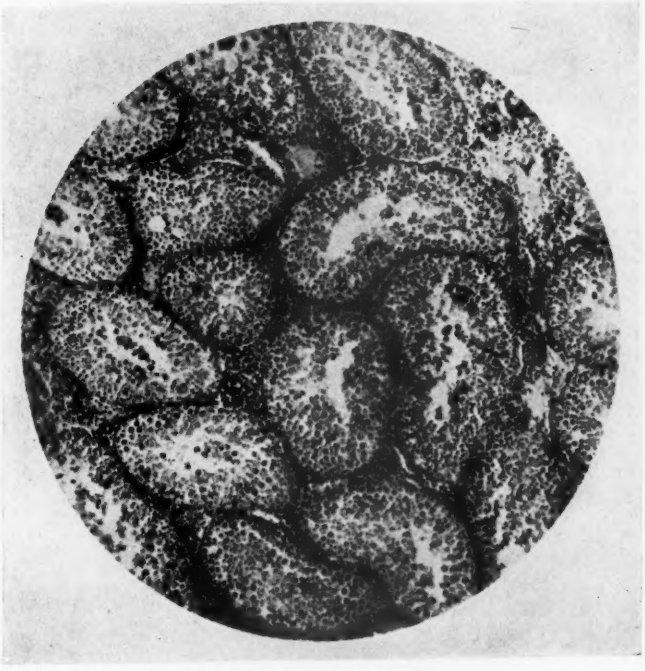

FIG 11

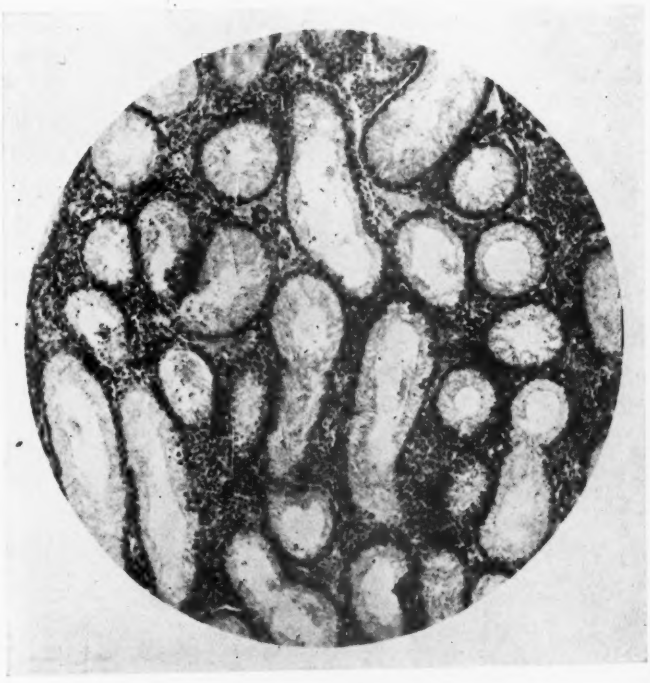

FIG. 12

FIG. 13. NORMAL TESTICLE

Section of right testicle of guinea pig F2 (×70), that is, of the mate to the left testicle pictured in figure 12. With care, spermatogonia, spermatocytes, spermatids and spermatozoa can be distinguished, in normal relationship.

FIG. 14. TUBERCULIN REACTION (AFTER 24 HOURS)

Tuberculin prepared from protein-free medium, consisting essentially of ammonium chloride, histidine dichloride, glycerol and salts. Guinea pig H1 (×275). Infected in left axilla with 0.1 mgm. tubercle bacilli of low virulence (R1), May 18, 1923; 0.01 cc. tuberculin from protein-free medium injected in left testicle, June 19, 1923. Guinea pig killed June 20, 1923. Gross picture at necropsy like figure 1. Similar injection of a noninfected guinea pig caused no reaction. Note hydropic degeneration of cytoplasm of spermatocytes, particularly in the tubule in the lower right quadrant, and the marked intertubular edema and infiltration of wandering cells. A mate to this guinea pig, similarly treated and allowed to live one month, showed the picture of figure 12.

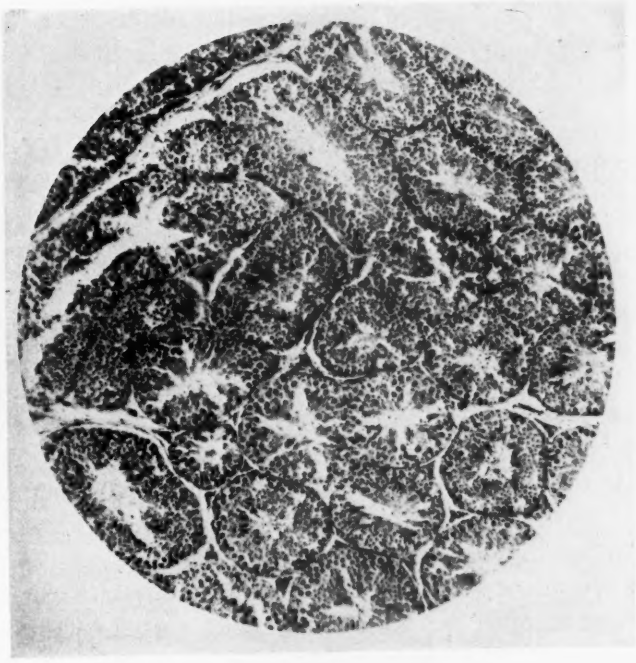

FIG. 13

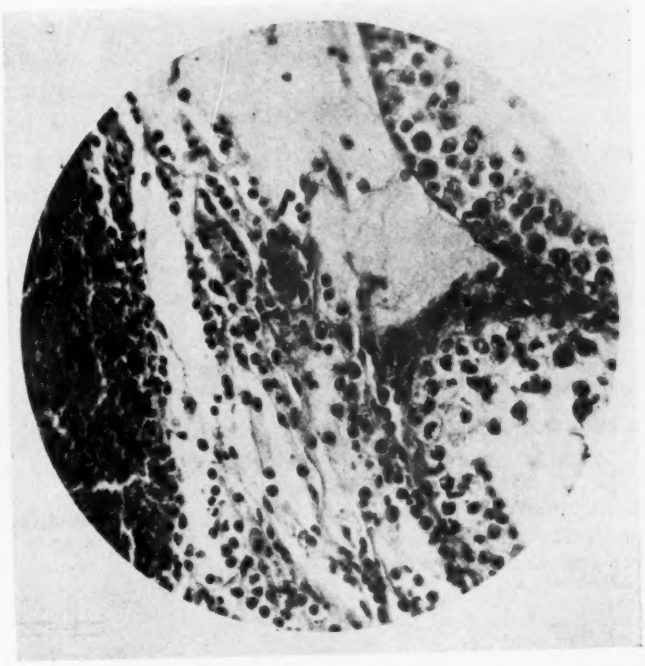

FIG. 14

THE TESTICLE AS AN INDICATOR OF ALLERGY IN THE HYPERSENSITIVENESS OF INFECTION AND ANAPHYLAXIS[1]

ESMOND R. LONG AND MAC HARPER SEYFARTH[2]

The tuberculin type of reaction, or the response in the hypersensitiveness of infection, and anaphylactic shock, the response of an animal sensitized to nonliving protein, once thought to have much in common, if not to be actually identical, have been sharply separated as distinct types of response in the broad field of hypersensitiveness. The reader is referred to Baldwin's (1) early work on the subject, to recent investigations by Zinsser (2) and M. I. Smith (3), and to numerous articles by Krause, particularly to a concise summary in the *Transactions of the National Tuberculosis Association* (4). The anaphylactic condition, its production, what must be included and what must be excluded under the term, and the distinction from anaphylactoid phenomena, have been recently treated in detail by Wells (5). A clear and convenient classification for the differentiation of forms of hypersensitiveness is given in an article by Coca (6).

The hypersensitiveness of infection is distinguished by these characteristics: the presence of parasites within the living body is necessary for its production, and a short time after infection has occurred the tissues of the infected body respond with acute, local inflammation to a fresh introduction of the infecting agent or certain products derived from it. The tuberculin reaction is the best known member of the group of reactions of this class, but the abortin, mallein, typhoidin, luetin and other reactions are probably of identical type. Because of the easy application of the skin test, cutaneous hypersensitiveness is commonly considered as the chief manifestation of the altered state.

It is a mistake, however, to think of the skin as more highly sensitized than other tissues. As has been suggested by Krause, probably in tuberculosis all tissues are sensitized to tuberculin. In the preceding

[1] From the Department of Pathology of the University of Chicago and the Otho S. A. Sprague Memorial Institute.

[2] Aided by a grant from the National Tuberculosis Association.

article Long (7) has described a testicle reaction, showing the exquisite sensitiveness of the germ cells of the tuberculous guinea pig, and the rôle which this sensitiveness plays in reinfection. In the present article we shall show (1) that tuberculins from nonprotein media are effective in eliciting the testicle reaction, (2) that a substance of tuberculin nature can be detected in other acid-fast bacilli by the testicle reaction, and (3) that the anaphylactic response and the reaction in hypersensitiveness of infection are entirely different in the testicle. An attempt to detect tuberculin in the urine of tuberculous patients (Wildbolz reaction), by means of the testicle reaction, is also described.

In order to save needless repetition, the protocols given below are in terms of the findings of the preceding article. At that time it was found that when tuberculin is injected into the testicle of a guinea pig with active tuberculosis a prompt reaction, reaching its height in 24 to 48 hours, occurs. If the guinea pig is killed within this period the injected testicle is found to be hyperemic and swollen; microscopically, there are interstitial edema and epithelioid and other wandering-cell infiltration, and the germ cells show remarkable degeneration varying from intracellular edema to necrosis, the spermatocytes and spermatids being chiefly affected. If the guinea pig is killed one month after the acute reaction a profound alteration in the condition of the testicle is found. It is decreased in size. The tubules remain, but are much smaller than normal, outlined merely by a basement membrane and ring of undifferentiated epithelial cells with filaments of detritus extending into the lumina; spermatocytes, spermatids and spermatozoa are no longer present. Between the tubules the interstitial cells of Leydig are found increased in number and epithelioid cells are numerous.

In the protocols these two pictures will be referred to as early and late tuberculin reactions of the testicle, with the further qualification of mild, definite or marked, to meet the requirements of the individual case. Guinea pigs were used and the sensitizing infections were made in the left axilla with 0.1 mgm. of R1, a tubercle bacillus of low virulence, about one month previous to the tuberculin experiments.

PROTOCOLS ON THE TESTICLE TUBERCULIN REACTION TO TUBERCULINS FROM NONPROTEIN MEDIA

These tuberculins were prepared by filtering through a Berkefeld filter two-months-old cultures of a moderately virulent tubercle bacillus, H37, on a medium consisting, in one case, of histidine, ammonium chloride, glycerol and salts (medium of Koessler and Hanke) and, in

another, of asparagin, glycerol and salts. Both tuberculins had the characteristic odor of tuberculin and a yellowish opalescent tinge; both gave the color reactions for proteins very faintly. One-tenth of a cubic centimetre of the unconcentrated tuberculin was injected directly into the left testicle. In each case two tuberculous and two noninfected guinea pigs were injected. One of each pair was killed after two days (or one day) and one after about five weeks. The gross appearance of the testicle was noted and microscopic sections were examined. The experiment was further controlled by injecting the plain histidine medium, in which tubercle bacilli had not been grown, into tuberculous and nontuberculous animals.

I1: Tuberculous guinea pig injected with 0.1 cc. histidine tuberculin. Killed one day later. Marked early tuberculin reaction in left testicle. Right testicle normal.

I2: Tuberculous guinea pig injected with 0.1 cc. histidine tuberculin. Killed two days later. Very marked early tuberculin reaction in left testicle. Right testicle normal.

I3: Tuberculous guinea pig injected with 0.1 cc. histidine tuberculin. Killed 34 days later. Typical late tuberculin reaction in left testicle. Right testicle normal.

II1: Noninfected guinea pig injected with 0.1 cc. histidine tuberculin. Killed two days later. Left testicle normal. Right testicle normal.

II2: Noninfected guinea pig injected with 0.1 cc. histidine tuberculin. Killed 34 days later. Left testicle normal. Right testicle normal.

III1: Tuberculous guinea pig injected with 0.1 cc. uninoculated histidine medium. Killed two days later. Left testicle normal. Right testicle normal.

III2: Tuberculous guinea pig injected with 0.1 cc. uninoculated histidine medium. Killed 34 days later. Left testicle normal. Right testicle normal.

IV2: Noninfected guinea pig injected with 0.1 cc. uninoculated histidine medium Killed 34 days later. Left testicle normal. Right testicle normal.

V1: Tuberculous guinea pig injected with 0.1 cc. asparagin tuberculin. Killed two days later. Very marked early tuberculin reaction in left testicle. Right testicle normal.

V2: Tuberculous guinea pig injected with 0.1 cc. asparagin tuberculin. Died of intercurrent infection 16 days later. Definite, though not marked, late tuberculin reaction in left testicle. Right testicle normal.

VI1: Noninfected guinea pig injected with 0.1 cc. asparagin tuberculin. Killed two days later. Left testicle normal. Right testicle normal.

VI2: Noninfected guinea pig injected with 0.1 cc. asparagin tuberculin. Killed 16 days later. Left testicle normal. Right testicle normal. (Young animal; neither testicle completely developed.)

The results indicated in the above protocols confirm those reported in the previous article. Tuberculin, prepared by growing virulent tubercle bacilli in nonprotein media, and filtering off the bacteria, like Old Tuberculin, is highly toxic to the testicular tissue of tuberculous guinea pigs, and quite nontoxic for that of nontuberculous guinea pigs. The effects upon the testicle are the same as those previously described, early hyperemia and swelling, with intertubular epithelioid-cell infiltration and degeneration of the germ cells, followed, in the course of a month, by absorption of the destroyed germ cells, with persistence, however, of tubules lined by undifferentiated cells, and with marked hyperplasia of the interstitial

cells. Control experiments showed the uninoculated culture medium to be absolutely nontoxic for either tuberculous or normal animal.

PROTOCOLS ON THE TESTICLE REACTION TO NONPATHOGENIC ACID-FAST BACILLI

Frog, grass, and smegma bacilli were injected into tuberculous and nontuberculous guinea pigs. The plan of the preceding section was used, guinea pigs being killed after two days and about four weeks, respectively, and examined for possible early and late tuberculin reactions. The injection was made in the left testicle as usual, and the designation of early or late tuberculin reaction in the protocols is made upon the basis of both gross and microscopic examination.

VII1: Tuberculous guinea pig injected with 0.1 mgm. frog bacilli. Killed two days later. Definite early tuberculin reaction in left testicle. Right testicle normal.

VII2: Tuberculous guinea pig injected with 0.1 mgm. frog bacilli. Killed 25 days later. Definite late tuberculin reaction in left testicle. Right testicle normal.

VIII1: Noninfected guinea pig injected with 0.1 mgm. frog bacilli. Killed two days later. Left testicle normal except for moderate wandering-cell infiltration; absolutely no degeneration of germ cells. Right testicle normal.

VIII2: Noninfected guinea pig injected with 0.1 mgm. frog bacilli. Killed 25 days later. Left testicle normal except for occasional atrophied tubule; no persistent cellular hyperplasia. Right testicle normal.

IX1: Tuberculous guinea pig injected with 0.1 mgm. grass bacilli. Killed two days later. Definite early tuberculin reaction with marked wandering-cell infiltration in left testicle. Right testicle normal.

IX2: Tuberculous guinea pig injected with 0.1 mgm. grass bacilli. Killed 30 days later. Very mild late tuberculin reaction in left testicle. Right testicle normal.

X1: Noninfected guinea pig injected with 0.1 mgm. grass bacilli. Killed two days later. Moderate wandering-cell infiltration but no tuberculin reaction in left testicle. Right testicle normal.

X2: Noninfected guinea pig injected with 0.1 mgm. grass bacilli. Killed 30 days later. Left testicle normal except that spermatozoa are far from numerous; the spermatocytes are normal. Right testicle normal.

XI1: Tuberculous guinea pig injected with 0.1 mgm. smegma bacilli. Killed two days later. Definite early tuberculin reaction in left testicle. Right testicle normal.

XI2: Tuberculous guinea pig injected with 0.1 mgm. smegma bacilli. Killed 30 days later. Definite late tuberculin reaction in left testicle. Right testicle normal. (Young guinea pig, not fully mature.)

XII1: Noninfected guinea pig injected with 0.1 mgm. smegma bacilli. Killed two days later. Left testicle normal, except for definite epithelioid cell and eosinophile infiltration; no degeneration of germ cells. Right testicle normal.

XII2: Noninfected guinea pig injected with 0.1 mgm. smegma bacilli. Killed 30 days later. Left testicle normal. Right testicle normal.

The results indicated in the above protocols confirm the experience of the previous article, with respect to the presence of tuberculin in nonpathogenic acid-fast bacilli and add new observations on the lack of pathogenicity or invasive power of these microörganisms, previously

noted by Krause and Baldwin. Unquestionably, something is present within the bodies of these acid-fast bacilli, frog, grass, and smegma bacilli, to which the tissues of the tuberculous animal are highly hypersensitive, which is quite without effect, however, upon the tissues of the nontuberculous animal. For the present we can simply designate the substance tuberculin.

In our experience the reaction of a normal animal to nonpathogenic acid-fast bacilli is very mild, consisting of a moderate infiltration of wandering cells of a variety of types, including not a few eosinophiles, without exudation of appreciable protein-containing fluid.

PROTOCOLS ON TESTICLE REACTION TO URINE OF TUBERCULOUS PATIENTS

Urine from one case of active, progressive pulmonary tuberculosis and from one case of quiescent pulmonary tuberculosis was injected intratesticularly into tuberculous and nontuberculous guinea pigs. An attempt was made to precipitate an active principle, acting like tuberculin, from the urine of the patient with progressive disease. The preparation injected was made by adding 80 cc. of 95 per cent alcohol to 15 cc. urine, letting stand, centrifugating and taking up the precipitate in 5 cc. distilled water. The urines are called *Hs* and *Fn* urines, and the precipitate is called *Hs urine precipitate.* The usual plan of injecting the left testicle and making examination after two days and about one month in tuberculous and normal animals, was followed.

XIII1: Tuberculous guinea pig injected with 0.1 cc. *Hs. urine precipitate.* Killed after two days. Left testicle normal, except for slight wandering-cell infiltration. Right testicle normal.

XIII2: Tuberculous guinea pig injected with 0.1 cc. *Hs. urine precipitate.* Killed after 32 days. Left testicle normal. Right testicle normal.

XIV1: Noninfected guinea pig injected with 0.1 cc. *Hs. urine precipitate.* Killed after two days. Left testicle normal. Right testicle normal.

XIV2: Noninfected guinea pig injected with 0.1 cc. *Hs. urine precipitate.* Killed after 32 days. Left testicle normal. Right testicle normal.

XV1: Tuberculous guinea pig injected with 0.1 cc. *Hs. urine.* Killed after two days. Left testicle normal. Right testicle normal.

XV2: Tuberculous guinea pig injected with 0.1 cc. *Hs. urine.* Killed after 32 days. Left testicle normal. Right testicle normal.

XVI1: Noninfected guinea pig injected with 0.1 cc. *Hs. urine.* Killed after two days. Left testicle normal. Right testicle normal. (Young, immature guinea pig.)

XVI2: Noninfected guinea pig injected with 0.1 cc. *Hs. urine.* Killed after 32 days. Left testicle normal. Right testicle normal.

XVII1: Tuberculous guinea pig injected with 0.1 cc. *Fn. urine.* Killed after two days. Left testicle normal. Right testicle normal.

XVII2: Tuberculous guinea pig injected with 0.1 cc. *Fn. urine.* Killed after 32 days. Left testicle normal; abscess in epididymis. Right testicle normal.

XVIII1: Noninfected guinea pig injected with 0.1 cc. *Fn. urine.* Killed after two days. Left testicle normal. Right testicle normal. (Young, immature guinea pig.)

XVIII2: Noninfected guinea pig injected with 0.1 cc. *Fn. urine.* Killed after 32 days. Left testicle normal. Right testicle normal.

About the only positive conclusion to be drawn from the above protocols on the injection of urine is that small amounts of urine are nontoxic to testicular tissue, either in immediate or late effect. The results are far from extended in their bearing on the Wildbolz reaction, but at any rate do not confirm Wildbolz's positive results on the presence of tuberculin in the urine of patients with progressive tuberculosis. *Hs.* was a patient of this class, but neither the undiluted urine nor the concentrated alcoholic precipitate from his urine had the slightest effect upon the germ cells of tuberculous guinea pigs, highly sensitive as our experiments have shown these cells to be. The urine of the patient with quiescent disease was equally ineffective.

PROTOCOLS ON TESTICLE REACTION IN ANAPHYLAXIS

Guinea pigs sensitized to gliadin and egg albumin were injected three weeks later with the respective antigens in the testicle. The effect of intratesticular injection of antigen in guinea pigs immunized against egg albumin by repeated weekly doses was also observed. The usual method of observing the two-day and one-month reaction was followed.

XIX1: Guinea pig sensitized to gliadin by intraperitoneal injection of 10 mgm., June 26, 1923. One milligram of gliadin injected into left testicle, July 17, 1923. Killed two days later. Left testicle normal, except for a definite wandering-cell infiltration; no degeneration of germ cells. Right testicle normal.

XIX2: Guinea pig sensitized to gliadin by intraperitoneal injection of 10 mgm., June 26, 1923. One milligram of gliadin injected into left testicle, July 17, 1923. Killed 32 days later. Left testicle normal. Right testicle normal.

XX1: Normal guinea pig. One milligram of gliadin injected into left testicle, July 17, 1923. Killed two days later. Left testicle normal, except for moderate wandering-cell infiltration. Right testicle normal.

XX2: Normal guinea pig. One milligram of gliadin injected into left testicle, July 17, 1923. Killed 32 days later. Left testicle normal. Right testicle normal.

XXI1: Guinea pig sensitized to egg albumin by intraperitoneal injection of 10 mgm., June 26, 1923. One milligram of egg albumin injected into left testicle, July 17, 1923. No immediate symptoms but death within 2 hours. Lungs distended with air; numerous discrete subpleural ecchymoses 1 to 2 mm. in diameter. Left testicle normal. Right testicle normal.

XXI1a: Guinea pig sensitized to egg albumin by intraperitoneal injection of 10 mgm., June 26, 1923. One milligram of egg albumin injected into left testicle, July 17, 1923. Killed two days later. Left testicle normal except for marked wandering-cell infiltration, including many eosinophiles. Right testicle normal.

XXI2: Guinea pig sensitized to egg albumin by intraperitoneal injection of 10 mgm., June 26, 1923. One milligram of egg albumin injected into left testicle, July 17, 1923. Killed 32 days later. Left testicle normal. Right testicle normal.

XXII1: Normal guinea pig. One milligram of egg albumin injected into left testicle, July 19, 1923. Killed two days later. Left testicle normal except for a moderate wandering-cell infiltration including many eosinophiles. Right testicle normal.

XXII2: Normal guinea pig. One milligram of egg albumin injected into left testicle, July 19, 1923. Killed 30 days later. Left testicle normal. Right testicle normal.

XXIII1: Guinea pig immunized against egg albumin by intraperitoneal injections of 10 mgm. on June 26, June 30, and July 5, and of 20 mgm. on July 10, 1923. One milligram of egg albumin injected into left testicle, July 17, 1923. Killed two days later. Left testicle normal except for very marked epithelioid and round-cell infiltration and slight eosinophilia; no degeneration of germ cells. Right testicle normal.

XXIII2: Guinea pig immunized against egg albumin by intraperitoneal injections of 10 mgm. on June 26, June 30, July 5, and 20 mgm. on July 10, 1923. One milligram of egg albumin injected into left testicle, July 17, 1923. Killed three months later. Left testicle normal except for slight interstitial hyperplasia and slight wandering-cell infiltration; no degeneration of germ cells. Right testicle normal.

The response of the testicular tissues to the antigen in guinea pigs sensitized to foreign proteins is thus seen to be entirely different from that seen in the tuberculin type of reaction. Introduction of egg albumin and gliadin into the testicle of guinea pigs sensitized to these proteins led, at the most, only to a moderate and transient interstitial infiltration of wandering cells. The germ cells remained quite unaffected. In no case did anything occur to suggest the presence of a cytotoxin in the injected organ, as was invariably noted in the tuberculin reaction. The mild mononuclear infiltration did not definitely exceed the similar response to intratesticular injection of these same proteins into normal guinea pigs.

We do not of course consider our experiments as very extensive on anaphylaxis. It is possible that proper dosage may not have been employed and proper sensitization not secured in all cases. Nevertheless, in one animal sensitization must have been of high degree, for this animal (XXI1) died within two hours after the second or shocking dose, in spite of the poor absorptive conditions afforded by the testicle, with the characteristic necropsy findings of anaphylactic shock. The case must have been one of unusually rapid absorption. There is no reason for believing that the other sensitized animals of the series were any less well sensitized than this guinea pig, inasmuch as they received the same sensitizing dose in the same manner.

We would not lay too much stress upon the eosinophilia usually noted. It was conspicuous in the response of the sensitized XXI1a, but almost equally prominent in that of the nonsensitized XXII1. At first we were inclined to attach considerable significance to this eosinophilia, which was noted frequently in the testicle tuberculin reaction, but we have since learned that many stimuli may elicit eosinophilia in the testicles of nonallergic guinea pigs, as, for instance, the injection of nonpathogenic acid-fast bacilli or egg albumin.

The guinea pigs immunized against egg albumin showed no highly characteristic response on testicular injection of the antigen. The wandering-cell infiltration in this case (XXIII1) was the most marked of the series, but no effect upon the delicate germ cells was observed. Altogether, in this series there was complete failure to demonstrate anything like the Arthus skin phenomenon in rabbits.

PROTOCOLS ON GUINEA PIGS SENSITIZED WITH TUBERCULIN

Two noninfected guinea pigs were injected intraperitoneally with tuberculin and 24 days later intratesticularly. They were killed and examined after two and eighteen days, respectively.

XXIV1: Guinea pig injected intraperitoneally with 0.1 cc. Old Tuberculin, July 19, 1923. One one-hundredth cubic centimetre of Old Tuberculin injected into left testicle, August 13, 1923. Killed two days later. Left testicle normal. Right testicle normal.

XXIV2: Guinea pig injected intraperitoneally with 0.1 cc. histidine tuberculin, July 19, 1923. One one-hundredth cubic centimetre of histidine tuberculin injected into left testicle, August 13, 1923. Killed 18 days later. Left testicle normal. Right testicle normal.

The above protocols are but one more confirmation of the universally admitted fact that tuberculin does not sensitize in such fashion that the animal later gives the tuberculin test. The anaphylactic condition might be achieved if the tuberculin contained protein, just as it might occur on sensitization with any other foreign protein, but an allergy of the type seen in the hypersensitiveness of infection does not occur. And the testicle, unlike smooth muscle, as far as our observations go, does not disclose the anaphylactic state.

PROTOCOLS ON TESTICLE ABORTIN REACTION

Guinea pigs infected with Bacillus abortus and noninfected guinea pigs were given intratesticular injections of a suspension of B. abortus, and killed after two days.

XXV1: Infected guinea pig given an intraperitoneal injection of one-sixth of an agar slant of *B. abortus*, August 7, 1923. One-tenth cubic centimetre of abortin (suspension of bacilli) injected into left testicle, August 24, 1923. Killed two days later. *Necropsy findings:* The left testicle is extremely hyperemic and partially adherent in its sac. There is a dark purple tumor mass in the epididymis. The right testicle is atrophied and contains a white glistening nodule in the upper pole. The spleen is twice normal size, and there are easily torn fibrous adhesions between spleen, left kidney and stomach.

Microscopic: Left testicle: there is marked degeneration of the tubular epithelium and a moderate wandering-cell infiltration. A hemorrhagic, granulomatous mass is present in the

epididymis. *Right testicle:* the tubular epithelium is degenerated but to less extent than in the left testicle. There is an abscess encapsulated in the tunica albuginea.

XXVI1: Normal guinea pig. One-tenth cubic centimetre of abortion (suspension of bacilli) injected into left testicle, August 24, 1923. Killed two days later. Left testicle normal, except for slight wandering-cell infiltration. Right testicle normal. (Young, immature guinea pig.)

That an abortin reaction, similar in type to the tuberculin reaction, may occur in the testicle of guinea pigs infected with *B. abortus*, is indicated by the above protocols. The results are obscured by the fact that the testicle seems prone to become infected anyway in the course of *Bacillus abortus* infection, at least when this is given intraperitoneally, a result noted in other animals than XXV1. We shall repeat this experiment, using subcutaneous infecting sensitization. The testicle reaction, as observed in the one case here reported, partook of the character of both early and late reactions of the tuberculin type, using these terms in the manner employed earlier in this article. Hyperemia and swelling were observed in the infected guinea pig on the testicular injection of abortin, and not in the normal guinea pig. But on microscopic examination a degeneration of obviously much more than two days' duration was observed, with both a granuloma and a fresh abscess in the neighborhood to account for it.

SUMMARY

1. Tuberculins prepared from a nonprotein medium, in which histidine, asparagine or ammonia supplies the nitrogen, elicit a marked reaction in testicles of tuberculous guinea pigs, entirely comparable to, if slightly less intense than that caused by protein-rich Old Tuberculin. The question of the protein or nonprotein nature of tuberculin is not settled by these experiments, as the preparations used appeared to contain traces of noncoagulable protein formed in two months' growth of the bacilli.

2. Frog, grass and smegma bacilli appear to contain tuberculin, as they cause a definite testicular reaction (as described by Long), with profound degeneration of the germ cells, in tuberculous guinea pigs.

3. Frog, grass and smegma bacilli have no effect upon the testicle of normal guinea pigs beyond a mild and transient wandering-cell infiltration.

4. Urine from tuberculous patients with progressive and latent disease has not been found to contain tuberculin or any substance causing reaction or degeneration of the germ cells of the testicle. Fresh urine appears to have no effect upon the normal testicle.

5. In contrast to the tuberculin reaction, there is no recognizable anaphylactic reaction in the testicle. When the antigen is introduced in the testicle of guinea pigs sensitized to foreign protein only a transient wandering-cell infiltration occurs. The germ cells are not affected. An eosinophilia occurs, but this is frequent in the guinea pig testicle in nonallergic conditions.

6. Tuberculin itself does not sensitize the uninfected animal so that it will give the testicle tuberculin test.

7. An abortin reaction, similar to the tuberculin reaction, has been obtained in the testicle of a guinea pig with *Bacillus abortus* infection.

8. The guinea pig testicle is useful in demonstrating the hypersensitiveness of infection. It does not indicate the anaphylactic state. In the testicle reaction for hypersensitiveness it is best to use guinea pigs of not less than 350 grams weight, as in younger animals degeneration of germ cells is not so conspicuous.

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CONCERNING THE PRESENCE OF A SPECIFIC ANTIGEN IN THE URINE OF PATIENTS WITH ACTIVE TUBERCULOSIS[1]

B. M. FRIED

Marmorek (1) first formulated the conception that in active tuberculosis the urine and blood serum contain a toxin secreted by the tubercle bacilli and detectable by the complement-fixation reaction. "We believe," said Marmorek, "that in activity the bacilli secrete a toxin that is different from tuberculin, and that it is this toxin, and not tuberculin, that should be investigated."

He employed the following technique: 0.15 cc. of an immune horse serum rich in antibodies, 0.2 cc. of filtered urine (supposedly antigen) and one drop of fresh undiluted complement (guinea-pig serum) were incubated for one hour at 37°C. To this mixture was then added three-tenths of a dilution of one to ten of sheep's red cells, and antisheep amboceptor in a quantity "just sufficient to hemolyze 0.3 cc. of red corpuscles in 45 minutes" (Marmorek, *l.c.*); and this was placed in an incubator for 30 minutes at 37°C.

Of 306 sera and 294 urines from tuberculous patients, the test, according to Marmorek, agreed with the clinical findings in 95 per cent of all cases.

The work of Debré and Paraf (2) differs from that of Marmorek in that (1) a specific antigen, but not a toxin, exists in the urine and (2) the test was performed only in patients with renal tuberculosis or, as they put it, they looked for the antigen "at the very level of the lesion" (*au niveau de la lésion même*).

In the test they used increasing quantities of urine (from patients with renal tuberculosis)—0.4, 0.6, and 0.8 cc., one unit of complement, and one unit of amboceptor. As a result of their extensive work, they concluded that "the antigen reaction has a real clinical value, being especially important in the diagnosis of early renal tuberculosis."

Inspired by the results obtained by Marmorek and Debré and Paraf,

[1] From the Department of Pathology, Harvard Medical School, and the Pathological Laboratory of the Boston Sanatorium, Boston.

Wildbolz (3) employed the urine from tuberculous patients as a tuberculin in intracutaneous tests for the diagnosis of active pulmonary tuberculosis. Only by concentrating the urine to one-tenth of its volume and the intracutaneous injection of one drop was Wildbolz able to obtain a skin reaction. (Wildbolz apparently conceived the idea of concentrating the urine to one-tenth of its volume from the technique employed in the preparation of old tuberculin in which the broth-glycerin culture is concentrated to one-tenth of its volume.) As a result of his work, he concluded that the test was always and only positive in active pulmonary tuberculosis, and negative in arrested and nontuberculous patients.

In the articles published recently in this country by Hayman (4), Korns (5) and Lewis (6), the reader will learn the clinical value of the test. The results obtained by the application of the test on a couple of dozen patients at the Boston Sanatorium are in complete agreement with the conclusions drawn by the above mentioned authors.

The purpose of this study was to verify whether the urine excreted by tuberculosis patients, and concentrated according to the Wildbolz technique, contains a specific antigen detectable by the complement-fixation reaction.

TECHNIQUE

Concentration of urine: An overnight specimen of urine (about 200 cc.) was concentrated in distillation flasks *in vacuo* under a pressure of 25 to 27 inches and at a temperature of 45° to 50°C. It was then kept on ice for 24 hours, and filtered to obtain a filtrate free from urinary salts.

Antigen: Each sample of urinary antigen was always titrated for its anticomplementary properties before the performance of the test. One-half of the anticomplementary unit, usually 0.2 to 0.25 cc. of concentrated urine, corresponding to 2 to 2.5 cm. of nonconcentrated urine, was employed. As can be seen, the amount of urine used is higher than that used by Marmorek and Debré and Paraf.

Antibodies: An immune horse serum rich in antibodies, furnished to me by Professor Besredka, was used. One-tenth of a dilution of one to ten thousand of the serum fixed 8 units of complement in the presence of one-sixth of the anticomplementary unit of Besredka's tuberculosis antigen (7).

Test: Four tubes were used in the test. Tubes 1 and 2 contained, each, concentrated urine equivalent to one-half of the anticomplementary unit, increasing quantities of complement (1½ and 2 units), four units of amboceptor, 0.5 cc. of sheep's red cells, and saline solution sufficient to bring the total volume to 2 cc. Tubes 3 and 4 served as controls and differed from tubes 1 and 2 in that they contained Besredka's bacillary-emulsion tuberculosis antigen instead of urine. The first incubation was 75 minutes at 37° C. in a water bath, and the second 30 minutes at 37° C.

MATERIAL

In all, 40 urines were studied. They fall into two groups. The first group consists of urines furnished by patients with signs of moderately or far advanced active pulmonary tuberculosis. The remaining 9 urines were secured from cases of renal tuberculosis proved by guinea pig inoculation.

In the first group, the immune horse serum fixed one and one-half units of complement in 4 instances (13 per cent), and 2 units in only one instance (3 per cent). Of the 9 cases with renal tuberculosis, fixation of the complement was present with $1\frac{1}{2}$ units in one instance, and always absent with the use of 2 units.

A careful study of these patients, whose urine gave a positive result, as well as a complete examination of their urine for specific gravity, salts, albumen, etc., failed to disclose any factor which may explain the reaction.

SUMMARY

Forty specimens of urine (31 from patients with active pulmonary tuberculosis and 9 from patients with renal tuberculosis) were concentrated to one-tenth of their volume in accordance with the technique described by Wildbolz. The complement-fixation reaction was performed with each sample of urine, which served as an antigen in the presence of an immune horse serum rich in antibodies. In only one instance the immune serum fixed, in the presence of the concentrated urine, 2 units of complement and in 5 it fixed $1\frac{1}{2}$ units. The remaining 34 urines were absolutely negative.

CONCLUSIONS

There seems to be, as a rule, no antigen in the urine of patients with active tuberculosis that is detectable by the complement-fixation reaction.

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THE TECHNIQUE OF ORAL THERMOMETRY

PAUL M. ANDRUS AND R. H. WALKER[1]

Inasmuch as we are accustomed to regard thermometry as one of the few exact procedures of every day medicine, an investigation into the accuracy of the data as obtained by routine technique becomes of interest.

Palmer (1), speaking of failures in diagnosis and treatment among the tuberculous, states, "I am forced to the conclusion that our unfortunate results are due in large measure to inaccuracy and neglect of very simple things, and to no single factor so much as to the faulty taking and recording of temperatures. . . . . I believe I am justified in saying that eighty per cent of tuberculosis patients under medical care are handled and discharged without definite knowledge as to whether they are febrile or afebrile."

The chief elements investigated by us have been, first, the accuracy of the instruments themselves, and second, the time necessary for maximum oral registration. The effects of eating, drinking, exercise, outside temperature, etc., are generally recognized and have not been given special attention other than to avoid them as possible sources of error in our work.

ACCURACY OF THERMOMETERS

Thermometers were tested in a large, constant temperature water-bath at about 99°F., against a finely graduated thermometer with American Bureau of Standards certificate. For testing, instruments were inserted through holes in a large cork so that the entire bulb was immersed. The cork apparently prevents rapid cooling of the surface in the area of testing. Immersion of groups of thermometers in close contact, and without the cork protection, gave most erratic results, apparently such as were observed by those who took part in a controversy carried on in the London *Lancet* in 1913 (2), (3), (4), (5), (6).

Instruments were of the best quality and of the standard one and two-minute variety. Each carried the manufacturer's certificate of guaran-

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tee to within 0.2°F. and certificates also stated that "the bulb is made of 'normal glass' which makes the thermometer unalterable for all time."

Thus, of two gross of high-grade, new, unused thermometers, 7 or roughly 2.5 per cent showed inaccuracies greater than 0.2°F. Of 419 thermometers, previously found accurate and after having been in daily use for three months or more, 11 were found to have errors in excess of 0.2°F., exclusive of a number of instruments that would not retain their maximum readings or that became too difficult to shake down. Among cheaper thermometers we have seen large numbers show inaccuracies up to 2.5°F.

Thus, it is apparent that even guaranteed thermometers cannot be relied upon as accurate when new, and that they may become inaccurate or mechanically defective after use.

TIME ELEMENT OF ORAL THERMOMETRY

The technique for obtaining records has been as follows:

(1) No observations were made within two hours of the last meal.

(2) Patients were in bed one-half hour before temperatures were taken.

(3) No drinking or smoking had occurred within one-half hour.

(4) Care was taken that the lips were kept tightly closed and that the bulb of the thermometer was kept well under the tongue.

(5) Readings were recorded at the end of each minute and the thermometer was maintained *in situ* until no rise had occurred for a full five minutes.

(6) Readings were made without removing the instrument from the patient's mouth, preliminary investigations having been instituted to ensure our ability to make accurate readings under these conditions.

(7) Subjects were on open porches, but not out-of-doors or exposed to sun or wind.

(8) The outside temperature was warm, the work being done in the months of July, August and September.

(9) High-grade thermometers of the one and two-minute variety were used and first tested for accuracy.

(10) To establish whether or not the data obtained were peculiar to tuberculous invalids, a series (20 per cent of the whole) consisting of children and of adults in the wards of a general hospital was similarly tested.

The above precautions observed, the time necessary to attain maximum readings has been studied.

It is, we believe, common practice among both the public and the medical profession to accept readings from thermometers purporting to register in one-half, one or two minutes, in the specified time.

One of us took occasion on a visit to a general hospital to time a temperature record made by a pupil nurse. The instrument was removed after precisely forty-five seconds.

We have been fortunate in receiving, as below, information from 32 American and Canadian sanatoria as to the time used for thermometry records:

(1) Three stated that only rectal records were used.

(2) Seven pointed out that the time should be doubled or more in cold weather.

(3) Twenty-nine giving the time for mouth readings were as follows: Two minutes, 4; three minutes, 7; five minutes, 15; ten minutes, 1; and fifteen minutes, 2.

Chart 1 illustrates the time required for maximum oral registration in 200 individuals under the conditions as previously outlined. The results in tuberculous invalids, children in a preventorium and the adult sick of a general hospital, were in no whit different, and we have therefore refrained from complicating our records by separating them.

It will be seen that at five minutes only 29 per cent of the persons studied had attained their maximum temperature elevation, and at ten minutes 84 per cent. Conversely, if the temperatures were taken for only five minutes we would fail to attain the maximum reading in 71 per cent of the subjects and, if they were taken for ten minutes, in 16 per cent. The occasional cases showing rise after fifteen minutes were advanced progressive tuberculosis patients and may be presumed to have had actual increase of fever during this period.

It will be noted that the curve reaches a peak at seven minutes. The six to eight-minute period represents 42.5 per cent of the total, and drops off rapidly in either direction.

The degree of increase obtained in the longer periods is of course of great importance. Of those readings taking over 5 minutes to attain a maximum, the average rise was slightly better than 0.3°F. This average is, of course, made low by the considerable numbers recording a maximum in 6 and 7 minutes and having therefore a relatively small increase. The maximum rise beyond the 5-minute period was 2.2°F.

Thirty per cent showed an increase of 0.4°F. or higher, an elevation sufficient to make the difference between the recognition or otherwise of fever.

Of those readings taking over ten minutes to attain a maximum, the average increase was exactly 0.2°F. The maximum rise after 10 minutes was 0.6°F., attained by 7 per cent of this class. Seventeen per cent showed an increase of 0.4°F. or higher.

We had thought that in the presence of fever the maximum would probably register more rapidly than in its absence. An analysis of the 25 per cent of the series who had temperatures of 99°F. and over,

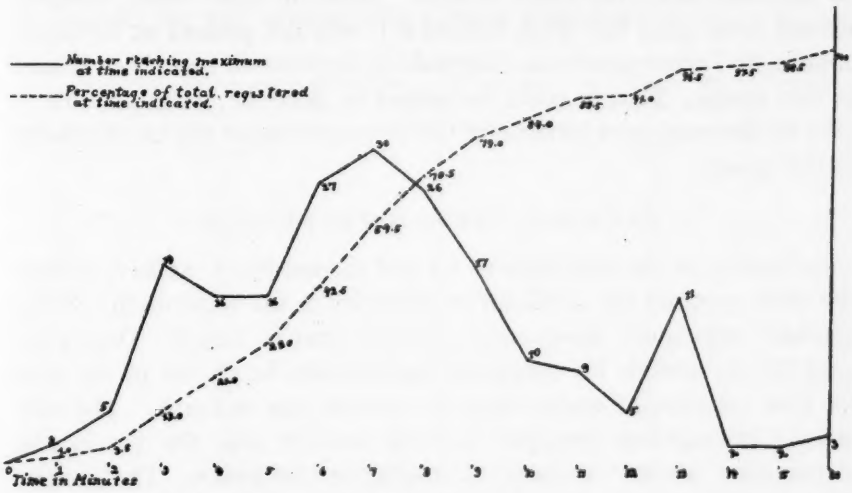

CHART 1. RECORDS OF 200 ORAL TEMPERATURES

shows that the converse is true. Thus, of this group only 16 per cent reached their maximum within 5 minutes, as compared with 29 per cent in the entire series; and 18 per cent took over 10 minutes, which was the same time as with those of all classes. Of those having fever and requiring over five minutes to register their maximum, the average increase was 0.4°F. as compared with 0.3°F. in the entire series. Of those with fever taking over ten minutes to register, the average increase was the same as for the entire series, namely, 0.2°F.

It must be recognized that the increase in temperature after the five and ten-minute periods, may, as far as the presence or absence of fever is concerned, be potential rather than actual, and that, unless the rise is

sufficient and within the particular range to change it from a non-febrile to a febrile reading, the increase becomes of secondary importance.

With this in mind we have studied our figures to ascertain how many came into this group. Of the 200 temperatures recorded, 53 showed temperatures of 99°F. or higher, and these we have classed as febrile. Of this group of 53, 13 were below 99°F. at five minutes and over 99°F. at the maximum reading, giving a total of 24 per cent of the febrile cases in which fever would have been missed if recorded for only five minutes. In like manner, if allowed to register for only 3 minutes, 42 per cent would have been missed. Of the febrile cases, 9 showed an elevation after the tenth minute. None of these cases, however, showed fever after the tenth minute if it was not present at the tenth minute, and consequently no diagnosis of fever would have been missed in this group. That it could be missed is, however, quite possible in view of the maximum increase of 0.6°F. present after the tenth minute in this group.

WATER-BATH VERSUS MOUTH READINGS

As bearing on the time element for oral thermometry, we have studied the time required for maximum registration in the water-bath. Fifty, one and two-minute instruments were accurately timed. They averaged fifteen seconds for maximum registration, being left in the bath for four minutes to ensure that no further rise occurred. The one-minute instruments averaged fourteen seconds and the two-minute instruments sixteen seconds, a negligible difference. The longest time was twenty-five seconds and the shortest eight seconds. This would appear to be corroborative of the statement of Frank Hayden (1) (apparently a manufacturer's representative) that, "Any clinical thermometer properly made will arrive at its maximum registration, under proper conditions of exposure or contact, within thirty seconds."

The reason for this discrepancy between the time required for water-bath and oral registration, although not material to the purposes of this paper, is nevertheless of interest. The most rational explanation would seem to be that the additional time for oral thermometry is necessary to allow the temperature of the mucous membrane of the mouth to approach that of the interior of the body. To this end we have examined a small series of patients by allowing the instrument to remain under the tongue for fifteen minutes; removing, shaking down and replacing without opening the lips; and recording the time necessary

for the instrument to regain the original reading. The results are as seen in table 1.

The relatively short periods for the second reading would seem to indicate that the above premise is probably true. The differences between these second readings and the time of water-bath registration (maximum of 25 seconds) is probably a question of contact.

We have observed that there is a correlation between the time required for recording and anatomic characters of the individual's mouth, namely, thickness of lips and cheeks and the depth of the sublingual cavity. Mary Williams (6) has recommended, apparently with good reason, that, when temperatures are taken in cold weather, "the neck and cheeks are well covered with a warm comforter."

TABLE 1

ORIGINAL TIME FOR MAXIMUM	REPEAT TIME FOR MAXIMUM
minutes	*minutes*
10	¾
10	2
11	1½
15	1
11	1¾
9	1½
12	1
13	1¼
13	3
2	1¼
8	2
17	4¼

We have also made a small series of observations as to the relative time of the recording of one and two-minute thermometers by mouth. This was accomplished by placing the two tested instruments under the tongue simultaneously. The time of recording has in each case closely approximated, each having on occasion required the longer time. This work, of course, lends itself to the criticism of inadequate contact.

ORAL VERSUS RECTAL THERMOMETRY

As previously mentioned, 5 out of 32 tuberculosis institutions advised us that only rectal temperatures were used.

Others have, however, indicated a preference for mouth records. One of our leading tuberculosis men stated, "for a time I tried to in-

stitute rectal temperatures, but this proved almost impracticable;" and another, "the oral temperatures, while having a different range throughout the day, were less variable for any given time than the rectal, and we felt that it was easier to follow the indications when taking temperatures by mouth."

Again Dr. A. M. Forster (1), in a discussion of a paper on thermometry, stated, "I feel that mouth temperature . . . . . is more dependable and gives a better idea of the changes in temperature due to tuberculosis than does the rectal temperature. In other words, the rectal temperature varies much more quickly and is much more sensitive to effects of digestion and of exercise than the mouth temperature is."

During the securing of the data given in the earlier paragraphs of this paper, although tedious alike to patient and operator, the subjects took marked interest in the work, and their coöperation was excellent. Attempts to make comparative rectal records, however, resulted for the most part in refusals. In the few comparative records that we have been able to obtain, the readings varied from agreement to a difference of one degree. The different texts similarly disagree on estimates of the normal difference between oral and rectal temperatures. Accordingly, it would seem to us that one difficulty in the adoption of rectal temperatures would be the necessity for establishing new standards of normal.

Aside, however, from the purely mechanical phase of the problem, we have no data on which to base an individual opinion.

Whichever of these methods is ideal, the fact remains that the large majority of workers are using oral readings and, until they can be converted to rectal usage, efforts toward standardizing mouth technique will fill a much needed place.

SUMMARY AND CONCLUSIONS

1. Even certified thermometers cannot be relied upon as to accuracy, and they may alter with use.

2. Two-minute thermometers require as long to register as do one-minute instruments.

3. Seventy-one per cent of tested persons failed to record their maximum temperature elevation by mouth in five minutes; and 16 per cent failed to record their maximum in ten minutes. Fifteen minutes by mouth in temperate weather is necessary to ensure maximum readings.

4. Twenty-four per cent of patients with fever failed to record fever in five minutes by mouth, while 42 per cent failed to register fever in three minutes.

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ANESTHESIA IN THE TUBERCULOUS

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Correspondence with approximately one hundred anesthetists, surgeons and internists especially interested in tuberculosis reveals a remarkable diversity of opinion on the question of the safety of inhalation anesthesia for surgical operations on those with tuberculosis. In this correspondence it was sought to procure the present view on this matter of those physicians and surgeons, whose residence in portions of the country to which tuberculosis patients resort would lead naturally to intimate association in a professional way with great numbers. In the aggregate, therefore, the views expressed are based upon a very large material and, inasmuch as the correspondence was addressed to prominent members of the profession, they may be regarded as sincere and of highly intelligent origin, notwithstanding their divergence. Opinions range from that of one surgeon who advocates the administration of ether as a cure for pulmonary tuberculosis to that of some internists and anesthetists who look upon the administration of ether in a tuberculous subject as unqualifiedly foolhardy.

It is of some interest that the anesthetists and tuberculosis experts to whom communications of inquiry were sent are, with few exceptions, more or less opposed to the administration of ether in the tuberculous. Surgeons, however, do not seem to have this distrust of ether. Many actually favor the employment of ether in this field of Surgery. For example, W. E. Savage of Cincinnati, in a paper read before the Ohio State Medical Association, May 15, 1917, attributed the recovery of tuberculous-peritonitis patients after laparotomy to the use of ether as an anesthetic. Savage sought to establish the view that recovery was brought about by ether anesthesia, owing to the small amount of oxygen in the blood during and following the anesthesia or as the result of some physicochemical change brought about by the presence of ether gas in the blood.

Savage employed ether anesthesia alone in a few cases of tuberculous peritonitis, early pulmonary tuberculosis and tuberculous pleurisy with

apparently good results. He takes the extreme position of advocating ether anesthesia in early tuberculous meningitis and concludes that respiratory disturbances are to be regarded as an indication for ether anesthesia rather than as a contraindication.

No other surgeon addressed seemed willing to endorse the views of Savage; however, the position of J. F. Baldwin of Columbus, Ohio, is typical of many. He says, "I have operated many times on more or less advanced cases of pulmonary tuberculosis and have never seen the slightest evidence of any trouble arising from its use."

Leonard Freeman of Denver remarks that both theory and experience lead him to believe that ether in itself does little harm in the tuberculous. If trouble results, which is seldom, it comes, he says, from other causes: from lowering of general resistance, due to the operation; from inhibition of pulmonary ventilation; from inability to clear the lungs by coughing; from stagnation of the circulation of blood and lymph due to prolonged decubitus.

W. W. Grant of Denver prefers to use gas and oxygen in active tuberculosis, but does not hesitate to give ether by the drop method in operations on patients suffering from latent tuberculosis. He calls attention to the use of local anesthesia in operations for tuberculous empyema. Apparently, he does not fear ether except in active tuberculosis, in the case of which he uses gas and oxygen.

John M. Foster, F.W. Kenney, C. E. Tennant and John F. Roe of Denver have no fear of harmful results from the use of ether in pulmonary tuberculosis if given by an expert anesthetist. Roe states that he has no hesitancy in using ether in all cases either active or latent.

W. A. Kickland of Fort Collins, Colorado, has in his experience found no case in which a latent condition of pulmonary tuberculosis was made active or an active case made worse by ether.

D. P. Mayhew of Colorado Springs does not fear ether in latent tuberculosis, and has the impression that the results obtained with nitrous oxide-oxygen, in so far as the pulmonary lesion is concerned, are no better than those obtained with ether.

C. B. Lyman of Denver has had no patient suffering with latent tuberculosis who has experienced a setback as the result of the administration of ether. He recalls some harmful temporary results after ether anesthesia in the active stage, but does not recall any case in which the damage was of permanent character.

F. H. McNaught of Denver has come to the conclusion that latent cases of tuberculosis are quite as safe for ether anesthesia as are the nontuberculous. He has observed a few cases in which an active process has been accentuated following the use of ether.

John E. Bacon of Miami, Arizona, records as his experience that a short ether anesthesia by the drop method does not often excite an active condition in latent tuberculosis of the lungs. He has been surprised at the lack of irritation in a few active cases in which he was obliged to give ether. Bacon cautions against the careless use of oxidized ether and advises that only the fresh product be used. On one or two occasions he has observed severe congestion of the lungs, bordering on bronchopneunomia, which he traced to the use of oxidized ether.

F. T. Wright of Douglas, Arizona, believes that ether can be used with safety in tuberculosis; and W. Wylie of Phoenix, Arizona, has used ether anesthesia almost exclusively for fifteen years and has thus far seen no bad results.

W. F. Glazier of Carlsbad, New Mexico, believes ether to be harmless in latent cases if the anesthesia is of short duration. He has used ether in active pulmonary tuberculosis without bad results.

C. J. McIntyre, internist, of Indianapolis, says that it has been proved that seventy per cent of the so called ether pneumonias are, in reality, infarcts of the lung. Positive evidence, he states, is yet to be produced, showing that ether activates pulmonary tuberculosis.

Anesthetists and internists seem almost unanimous in their opposition to ether in tuberculosis. Thus, J. T. Gwathmey of New York says that it is the opinion of those in charge of tuberculosis camps in his vicinity that ether, given by inhalation to tuberculosis patients, sends them to their graves in less than six months. Nitrous oxide and oxygen is the usual method of anesthetization in the Eastern institutions. Ether can be given, however, he says, with perfect safety to tuberculosis patients if the oil-ether colonic method be used. He has used it in this way, personally, in the tuberculous and has never seen any bad results from it.

E. I. McKesson of Toledo, Ohio, never uses ether in surgical cases complicated with tuberculosis, since, as he says, there are doubtless possibilities of pulmonary irritation with this anesthetic.

C. N. Combs of Terre Haute, Indiana, in an experience of nine thousand general anesthesias, has had very few pulmonary complications.

L. L. Miner of Tyrone, New Mexico, condemns chloroform but can recall no instance of unfavorable results from ether in the tuberculous. He uses a mask with a coil attached, permitting hot water to flow through it. He would be afraid of cold ether in such cases.

E. R. Baldwin, of the Trudeau Foundation, states that he is glad to give his testimony against the use of ether in all active tuberculosis cases and, so far as is possible, in known latent or recently arrested tuberculosis. The sequence of events, he says, has in too many instances convinced him of the baneful effects of profound etherization in activating tuberculosis, and he would not be one likely to consent to operations for which this anesthetic is deemed necessary by the surgeon.

Lawrason Brown, of Saranac Lake, New York, states that several years ago he, with Petroff, did some experiments, observing the effect of ether on guinea pigs. He states that they were unable to show that it either hastened or retarded the tuberculosis. Personally, he advises his patients to take nitrous oxide and oxygen, using ether, if at all, for the relaxation of spasm at the height of the operation. He believes that it is the way in which the ether is administered, rather than the effect of the ether itself which produces the injurious results when they arise.

John Morgan of Rochester, New York, has come to the conviction that ether should never be given to a latent, active or suspected tuberculosis case. The danger of immediate damage is great, and much remote trouble is directly traceable to the administration of ether. Unfortunately, he continues, most anesthesia records terminate with the patients' dismissal from the hospital in good condition, but if the patients should develop active tuberculosis in two years, he would feel that ether, if administered, was to blame for it.

James Alexander Miller, of New York City, states that it is his practice not to give ether to any cases that have either active pulmonary tuberculosis or that have recently been active. In cases that have become definitely arrested, in which the lesion is very small and the desirability of ether anesthesia great, he has often consented to its use, though he regards it much safer to use other forms of anesthesia in cases where there is any suspicion of tuberculosis of the lungs.

E. K. Richard of Rochester, New York, reports as follows:

(1) In taking histories of patients at Trudeau, I not uncommonly was forced to the opinion that a general ether anesthesia was "the match that lit the fire." Without recourse to records, I can think of three patients by name in which this was true. The experience was common at Trudeau.

(2) In my general hospital work, taken after my residenceship at Trudeau, I have seen a number of cases of general surgical disease (nontuberculous) become active cases of pulmonary tuberculosis following ether anesthesia. In fact, only recently a surgical case died within three months after operation, of pulmonary tuberculosis undoubtedly activated by the ether anesthesia. Careful history taking and careful physical examination made *ante operationem* has revealed to me past or present tuberculous disease manifestations so often that I am impressed with the extreme importance of such analysis on all cases requiring anesthesia. Too often this is neglected, to the surgeon's shame.

Since time and circumstance usually do not give the average surgical case such painstaking ante-operative analysis, and since tuberculosis, latent or active, is so omnipresent, I am firmly convinced that, wherever possible, gas and oxygen anesthesia should be used in all cases not so thoroughly examined. Further, the presence of active or healed organic tuberculosis anywhere in the body should be a contraindication to ether anesthesia. Where we encounter the history of past or present fistula, pleurisy, chronically discharging ear, etc., we must be unusually cautious.

Even in cases where there is no evidence of tuberculosis, I advise against ether on general principles. It is a safe rule and protects the patient.

J. J. Lloyd of Rochester, New York, states that he feels very strongly that ether is contraindicated in all known cases of tuberculosis, whether latent or active. He says that he has seen a great many acute exacerbations following operations under ether which pursued an unfavorable course. Of course, he adds, it is impossible to separate from the ether the shock of the operation and the convalescent period. He remarks that the bad results in operations under ether are not always noticeable until some time has elapsed after the operation. He regards novocaine as the anesthetic of choice and gas-oxygen next.

Lee Adrian Whitney of Rochester, New York, says he has not used ether anesthesia for the past eight years in any of the tuberculous bone and joint cases which have come under his direction. His experience had been very unfortunate with ether in tuberculosis cases, several having died each year as the result of miliary tuberculosis, following the administration of ether. In other instances there was a lighting up of pulmonic lesions. For the past eight years he has used gas-oxygen only in all work, tuberculous or nontuberculous.

E. S. Welles, Saranac Lake, New York, says that it is the rule in the general hospital of Saranac Lake never to give ether to patients who are suffering from active or latent tuberculosis. "The majority of my major operating," he says, "is done under combined novocaine and gas-

oxygen." It has been his conviction that ether anesthesia is bad for tuberculous lungs.

An exception to the rule that surgeons do not fear ether in tuberculosis is H. M. Wetherill of Denver. Wherever and whenever possible he uses local-infiltration anesthesia, associated with atropine or scopalamine. Next in safety, he says, comes spinal anesthesia and after that, for short operations, chemically pure sulphuric-ether anesthesia, preceded by small doses of morphine and atropine. For tuberculosis cases, nitrous oxide gas would have a small place in his armamentarium and chloroform would be absolutely barred. He regards chloroform as a deadly poison in such cases and quotes Harold Styles in his support.

C. D. Lockwood of Pasadena, California, a surgeon, occasionally uses ether with caution, but prefers gas-oxygen or local anesthesia in the tuberculous.

Wesley Bourne of Montreal, Canada, says concerning the advisability of giving ether to either active or latent tuberculous patients that, in the main, he believes ether to be especially contraindicated and should be used in diseases of the respiratory passages only when no other anesthetic is available. Gas-oxygen is his anesthetic of choice, but he says that there are many surgical procedures complicated by pulmonary lesions in which regional anesthesia may be the advisable choice.

R. C. Matson of Portland, Oregon, sees no reason why ether should not be given in latent tuberculosis. He opposes its use in all cases of open pulmonary tuberculosis. The great danger of ether anesthesia lies in its influence on the bronchial mucosa whereby secretions are stimulated, thus greatly enhancing the danger of aspiration infections.

J. B. Hartwell of Colorado Springs has a very vivid recollection of two patients in the Massachusetts General Hospital who were operated upon under ether anesthesia for tuberculous cervical adenitis and who died within a year after operation from miliary tuberculosis. Since that time he has not knowingly operated on a patient with acute pulmonary tuberculosis under ether anesthesia, preferring gas-oxygen or local anesthesia. He does not hesitate to use ether for short operations in arrested tuberculosis. He says, moreover, that patients with active tuberculosis, whose operations have been done under gas-oxygen, have often shown increased chest signs during the first ten days or two weeks after operation.

Gerald Webb of Colorado Springs says that even gas-oxygen may be followed by an acute upset if used in tuberculosis cases. It is his

rule to avoid, in every way possible, any operation requiring inhalation anesthesia in acute tuberculosis.

Lloyd Allen of Colorado Springs says that a general anesthetic is a grave insult to offer to an actively diseased lung. He feels that nitrous oxide gas is the anesthetic of choice in all patients with pulmonary tuberculosis when it is not possible to complete the operation with local-infiltration anesthesia.

C. E. Richmond of Colorado Springs advises against etherization in active cases, but believes that the danger of ether has been exaggerated.

W. T. H. Baker and William Senger of Pueblo, Colorado, working in different institutions, both say that it is their rule not to give ether to the tuberculous. Both prefer local or spinal anesthesia.

L. S. Peters of Albuquerque, New Mexico, is absolutely opposed to giving ether to either active or latent tuberculosis cases. Almost all of his operations are done under local anesthesia, and gas-oxygen is employed if a general anesthetic is necessary.

W. A. Gekler of Albuquerque, New Mexico, opposes inhalation anesthesia, especially because of the possibility of the aspiration into a still healthy lung of infected material during complete anesthesia. He says that he has had a number of patients who date the onset of their tuberculosis from some procedure under ether. He says, however, that he is not at all sure that the operation itself is not the exciting factor in many instances rather than the particular anesthetic agent used. He uses local anesthesia wherever possible.

Willard Smith, W. O. Sweek and E. P. Palmer, working independently at Phoenix, Arizona, are all opposed to the use of ether in the tuberculous. Palmer uses gas-oxygen when a general anesthetic is necessary. Smith also uses nitrous oxide-oxygen. Sweek condemns all inhalation anesthesia in the tuberculous, depending upon local anesthesia altogether.

F. R. Winslow of Hayden, Arizona, Meade Cline, S. A. Watson and Jeremiah Metzger of Tucson, Arizona, and Clarence Gunter of Globe, Arizona, say that it is against their experience and judgment to use ether where there is evidence of old tuberculosis. It is unjustifiable in active cases.

C. E. Yount at Prescott, Arizona, has practically abandoned inhalation anesthesia in the tuberculous. He is doing more and more work under local and spinal anesthesia. He says also that he has discontinued the use of ether colonic anesthesia.

Charles L. Minor of Asheville, North Carolina, allows no patient to be given ether and is entirely satisfied with gas-oxygen or regional anesthesia.

A. T. Pritchard of Asheville, North Carolina, says that he feels sure that on several occasions the use of ether and chloroform in the tuberculous, especially in latent infections, has not been followed by untoward effects. However, in active tuberculosis he regards nitrous oxygen as the anesthetic of choice.

F. W. Griffith of Asheville, North Carolina, prefers local anesthesia, but does not hesitate to give ether if he feels that the work cannot be done thoroughly under local anesthesia.

J. W. Pettit of Ottawa, Illinois, opposes ether in pulmonary tuberculosis if its use can be avoided. He is not so sure about the danger in latent tuberculosis.

George T. Palmer of Springfield, Illinois, says that he has become profoundly convinced that the administration of ether to a patient either suffering from active tuberculosis or a patient apparently arrested is an extremely hazardous thing.

John H. Peck of Des Moines opposes the use of ether in active tuberculosis, but would sanction its use occasionally in latent cases if given by a thoroughly trained anesthetist.

J. S. Pritchard of Battle Creek, Michigan, says that he has seen enough bad results in lung conditions following ether anesthesia to make him hesitate before allowing its use.

R. M. Waters of Sioux City, Iowa, prefers gas-oxygen to ether. In most instances, however, in which there is need for haste, ether may be necessary, though he prefers not to use it. He says that he would be much more particular as to the ability and good judgment of the man who used the anesthetic than as to the drug used.

F. J. Nordby and W. R. Abbott, both of the Public Hospital Service (Reserve), oppose ether unless absolutely necessary.

J. J. Buettner of Syracuse, New York, advises against the use of ether in either active or latent tuberculosis. He prefers gas-oxygen, skilfully administered. He believes that the length of the operation and the amount of ether used have a definite bearing on the postoperative sequellae.

J. H. Evans of Buffalo, New York, would not advise giving ether to tuberculosis patients. He has often operated under gas-oxygen with no apparent harmful results.

T. B. Smith of Wilmington, California, opposes ether in active or latent tuberculosis. He says that he believes that the tuberculosis specialists of the Southwest would all oppose ether.

F. M. Pottenger of Monrovia, California, believes that ether exercises a solvent effect upon the lipoids of pulmonary cells.

C. F. Hegner and O. S. Fowler of Denver oppose ether in tuberculosis and emphasize the point that it is the tuberculosis specialist rather than the surgeon or anesthetist who observes the ill effects of general anesthesia in these patients, because he cares for them and studies them for years whereas the others observe them for a brief period only.

It is unlikely that ether anesthetization by inhalation will ever be generally exonerated of its uncertain reputation in the tuberculous. It seems fair to say that very great care should be exercised in its use at present. Gas-oxygen, combined with local anesthesia, especially by nerve blocking, seems to have considerable standing as a much safer agent. It certainly seems reasonable to assume without question that a nonirritating, inhalation anesthetic has manifest advantages over ether in the tuberculous. Whether the unfortunate results following operation on the tuberculous are due to shock, pulmonary infarcts or the lowered metabolic activity accompanying any general anesthetic, surely we are giving the patient the full benefit of all doubt if we refrain from the use of ether by inhalation and use the nitrous oxide in the rare instances in which regional anesthesia does not suffice.

When prolonged anesthesia is necessary, and the surgeon is not accustomed to the use of local infiltration or nerve blocking, the method of ether-oil colonic anesthesia deserves attention. It is true that the ether used rectally is eliminated largely by way of the lungs but not in the high concentration necessary with inhalation anesthesia.

The writer purposely refrains from drawing conclusions from the opinions expressed by the representative correspondents quoted above. Their statements speak for themselves. However, it should be noted that the tuberculosis experts or internists residing in the most active fields of tuberculosis care and treatment, who live with these patients and study them for years, are almost with one voice against general anesthesia. A number of these have spoken of the onset of the disease being occasionally coincident with ether anesthesia. It is to be expected that surgeons will attach much value to the testimony of this group. It may not be presumptuous to say that such wide disparity of view upon this subject, as expressed by so many competent observers, tends to leave the surgeon of average experience in a somewhat doubtful state of mind with relation to the problem. As a practical observer he may be pardoned for assuming an attitude of cautious conservatism; and he will be acting, so it seems, quite sensibly if he addresses his interested attention to the generally acknowledged fact of the comparative safety of nitrous oxide gas and oxygen in surgery for the tuberculous and to the almost absolute safety of regional anesthesia in this field.

THE RELATION OF THE NATIONAL TUBERCULOSIS ASSOCIATION TO MEDICAL RESEARCH IN TUBERCULOSIS[1]

EDWARD R. BALDWIN

The Apostle Paul gave us a most appropriate text in his first letter to the Corinthians, which I venture to use as befitting this subject and occasion:

For we know in part and we prophesy in part. But when that which is perfect is come, then that which is in part shall be done away.

There have been many illustrations of the prophetic quality of these words, but no more in theology than in medicine.

We have indeed trodden a dark and painful path, and at a slow pace, yet illumined now and then by a bright light of discovery. How often have we been misled by our half-knowledge and false prophets. It is barely one hundred years since Laennec's time, when the study of tuberculosis was begun. Less than fifty years have passed since authority rather than fact-finding prevailed in the wards of hospitals.

Who indeed does not quote medical authority to-day, when a diligent inquiry into the basis for the statements, opinions or deliverances of our authorities would be humiliating?

Briefly stated, we know too little, and from this little "we prophesy in part." How often the little is magnified and established too soon in our minds and prematurely governs our acts—and policies! Then a more perfect knowledge is revealed, and the habits and customs firmly established are uprooted with difficulty. And here there is pride to be overcome,—pride of opinion, of past accomplishment or of a minor triumph.

On the other hand, the rapid gains in knowledge due to scientific methods have brought us far along the pathway toward the conquest of disease. Some there are who will be satisfied with the distance we have already gone. They argue that the main facts about tuberculosis are known. If things of major importance are already known why strive

[1] An address delivered before the Advisory Council of the Twentieth Annual Meeting of the National Tuberculosis Association, Atlanta, Georgia, May 7, 1924.

further, when we do not apply the facts already clearly shown to be true about disease? This is undoubtedly an exasperating reality. We do not apply them, and our science is leagues ahead of its application. But, I submit, this is no reason for self-satisfaction, or for discouragement and the return to inaction by stopping research.

The experimental method has been applied to every side of man's daily life until its results compel new adjustments, upset preconceived ideas and assail his peace of mind. We simply are unable to keep up with the multitude of discoveries or make a logical use of them within a reasonable time. The X-ray is an illustration, which, like the microscope of thirty years ago, is still beyond the reach of many who need its aid. Take the discovery of radium, of antitoxins and of insulin. They are all triumphs of experimental research, are now indispensable and, with every modern public and private facility mobilized, they can be widely used. It is nevertheless true that for thousands of human beings they must remain inaccessible, or unknown altogether for years to come. Moreover, many of the really valuable discoveries of medicine are being discarded already because of improved methods, simplifications or refinements. They are not unlike the useful automobile of a decade past: better service, more power or greater ease can be secured by scrapping the old machine.

I could go on with many examples, frequently experienced by all of us and including food, raiment and shelter. However, let me turn to the discovery of the tubercle bacillus, and point to the fact that forty-two years have passed yet the knowledge remains unutilized to a great extent.

The habits of a people are not easily changed, as we well know from experience with laws designed to govern them. Yet we fully believe that, with whole communities and nations already educated to the danger of tuberculosis from carelessness with sputum, a measurable decrease in the amount of infection has taken place, followed by a lessening of the disease no doubt directly due to this cause alone.

No one can doubt that the decrease might be greater if the sanitary care of sputum were more perfect. It may never be practicable or humanly possible to reach perfection; hence science must look further for means to control the disease. The present satisfactory fall in tuberculosis mortality is only an encouragement to further research, and should not be an excuse for inaction. Infection is still excessively frequent and but for improved social conditions might continue to take a high toll of tuberculosis deaths as is true now in Europe.

Another illustration of the impossibility of accomplishing what we know to be desirable is the eradication of tuberculosis in cattle. The impracticability of killing all the tuberculous cattle, as first advocated, has now become recognized and a workable but slower method has been adopted, based on the principle of isolation and quarantine or the so called "accredited herd" plan.

Logically, we should take advantage more generally of the most useful discovery by Pirquet, the tuberculin skin reaction introduced twenty years ago. We may well argue, that all children under five years of age should be tested, and, whether ill or not, should be carefully watched to avoid the possible future development of manifest tuberculosis. We can visualize many advantages from such knowledge. Whether we apply it or not will be still another problem, but it is evident that everywhere we turn research leads the way, and the whole structure of this great national organization against tuberculosis must be built on the facts that develop out of it.

When we mention research it is needful to take the broadest conception of that term. Knowledge gathered in any field may contain important truths for tuberculosis, especially that gained in the study of other infectious diseases. Thus, as we climb step by step to higher planes of knowledge our perspective widens and we see the dependence of research in tuberculosis on investigation in other sciences.

In fact, the progress toward the solution of many problems waits upon discoveries in chemistry, physiology and pathology. Thus, while busily engaged in tilling our part of the field, we must constantly watch that of our neighbors. It was certainly to our advantage that Pasteur was not a physician. He gave to the world of medicine more, possibly, because of that fact, for his mind and thought were unfettered, and immunology was born in the face of medical opposition,—practically created by a chemist as a side line.

In the present age of specialization we must admit that such events will be less likely to occur in the future, but the possibility of important contributions from outside our special domain to the scientific knowledge of tuberculosis should be kept in mind. This thought was admirably put by Mr. Homer Folks at the last meeting of this Association when he said that "there is a very close kinship between all the sciences, and the further their mysteries are penetrated the more general they become," and that the "antituberculosis movement is so broad and affects so many aspects of life, and so intimately, that we may lose sight of the fact

that it involves not only medicine, but also many-sided sanitation, vital statistics, economics, social work, political science, psychology and pedagogy, to mention only a few factors, and that in each of these lines, it is just as necessary, as it is in medicine, ... that we be guided by the scientific spirit." I would add that, to have this guidance, research and experiment are necessary. It is to the credit of this Association that such research has been promoted by it, and is being continued.

I would make the same plea that was voiced by Dr. Lawrason Brown in his presidential address last year; that the influence and resources of the Association be mobilized so far as possible to this end.

We need not fear too great changes in the program of the preventive campaigns, and yet in order to progress some experiments must be tried that are barren in results.

No doubt, to most of us experimental research means something done in a laboratory. Thus far the Research Committee has focussed on work of this kind which could be done with little expense and bring quick returns. I think the assistance given to workers in university laboratories the very wisest use of the funds thus far available.

This policy calls for little or no new equipment to be provided by the Association, and the work is done under experienced teachers who can direct and stimulate students in their chosen subject. Yearly or short term stipends are likely to arouse only a transitory interest for the most part, because of uncertainty as to the future. Something stronger is needed to appeal to the capable laboratory leaders than the casual interest of university authorities, who have questions of equal magnitude and greater attractiveness to occupy their attention. Possibly, if tuberculosis were as painful and dreaded as cancer, more resources would be at hand to study it. It has been neglected by comparison, and virtually left to the victims of the disease to find a way to their own salvation. This may be good policy in order to secure continuity of effort, and much gracious recognition has been vouchsafed those who have taken up the task and have been duly grateful for opportunities to work under their affliction. It will be easily recognized that large sums in the form of endowments or annuities should be available to secure continuous study of diseases like cancer and tuberculosis; diseases whose causes are so intimately connected with our habits and environment and affected by hereditary influences.

A bit of work here, another there, may and does have value, but a generation may pass before a comprehensive experiment can be completed.

Let this fact be widely known to thoughtful persons. Let us all contemplate what has been accomplished, and the futility of trusting to a flash of genius to solve all the problems in tuberculosis. It has been hard, plodding work, the "infinite capacity to take pains" that produced the best we have from Villemin, Pasteur, Koch and Theobald Smith. Two commissions, British and German, took ten years to settle the disputed question as to the importance of bovine tuberculous infection in man. Even this long and expensive work left unsolved the mystery of the absence of bovine tuberculosis in the human pulmonary disease of adults, one of the problems about which we seek more light to-day. We do not get results quickly in tuberculosis experimentation; that is, those workers who deserve credit for completing their studies do not expect any short cuts to help them.

The demand for quick results is compelling in America; and few have the courage or patience to withstand the pressure for premature publication. Whether it concerns an isolated, relatively unimportant problem, or is a fragment of one of the larger ones, such as a specific method of treatment, it must be left half done. Now this is necessarily true because we have not in the past commanded the resources or had the understanding support of governmental or private agencies. Our literature is well stocked with "preliminary reports" which fail of confirmation or completion, nor is it all the fault of the contributors.

The desire for recognition is honorable, and the trustees of institutions naturally wish to have lustre shed upon their departments engaged in research work.

What is more natural than undigested, unconfirmed and uncontrolled quantity production? An accumulation of chaff is already the fruit of several decades of futile and interrupted work, whereas if we are honest we shall repudiate it.

It has been the best that workers in tuberculosis could do with the time or money allotted to them by a utilitarian generation seeking for the sign of a cure.

What appears to me at present a waste of good material, through lack of sufficient support, might be made an asset to the knowledge of tuberculosis by providing stipends for five or ten years, either at universities or well-placed hospitals or sanatoria. Furthermore, the recipient of such a

stipend, be he teacher or student, should be of tested quality in some branch of science. It is unlikely that an impatient worker would accomplish much in tuberculosis, and he would be tempted to desert his problem for others promising quicker results.

After all the progress that has been made in the face of difficulties, it is perhaps unfair to decry the results. Much groundwork has been cleared in our knowledge of infection, resistance and experimental therapy. Whoever begins work to-day on a laboratory problem will save much time formerly lost in learning methods of approach. A few experienced teachers can be depended upon who have this knowledge, but truth is ever elusive and fact-finding is perpetually expanding it.

To the thinking investigator the explanation of experimental results is ever in need of amplification, and science seems to have no absolute, no final answer, yet it may furnish us with a practical working basis for action. We need not doubt, for example, that most persons possess some resistance to tuberculosis because they already have become slightly infected, although some develop the disease without apparent reason in spite of this. The value of the main fact is nevertheless of immense social importance, as well as epidemiological relationship.

The worker in tuberculosis must expect disconcerting things,—real paradoxes that lack explanation in the deeper sense and which reveal human fallibility. This is often illustrated in the false interpretations of alleged cures and the popular demand that they be tried, when no scientific evidence is offered that even the diagnosis of the alleged tuberculosis was ever made.

The eager public demands of us to give them a reason for an unexpected recovery under the use of a vaunted remedy. A coincidence may be incautiously suggested, but usually ridiculed as medical prejudice. Likewise, in much of the scientific work in medicine such contradictions tend to mislead us. It is only by facing these difficulties,—without which we might lack discipline,—that the study of tuberculosis will become one's chosen life work. There is need of more life workers in this field, and they must be content with the work for its own sake, so far as any certainty of discoveries of immediate importance are concerned.

The person with an eye single for the ultimate conquest of the disease must contribute his share and have the satisfaction that comes from faithful performance.

Others should not disparage such apparently barren efforts, for in their failure to comprehend the value of the experimental methods they are really turning the clock back.

The members of this Association can be of much service in favoring progressive work of all kinds, whether it be a new method to be tried in health education which will be experimental, or clinical and laboratory investigation, wherever they can best be carried out.

Experience in this country indicates that, with the exception of a few institutes which support full-time directors of clinical and laboratory work in the larger cities, sustained interest in the study of tuberculosis is chiefly to be found in health resorts. There are, no doubt, many advantages and some disadvantages in this situation; but the fact remains that in colonies of the tuberculous and in sanatoria it is possible to find the workers who need encouragement and support.

There is another reason for fostering experimental research on tuberculosis in sanatoria, and this is to keep up the interest and develop the taste for study among the medical staffs. There are no opportunities in many institutions situated at a distance from educational centres, and they need this stimulus.[2]

It seems to me that it is after all one of the functions of this Association to discover and develop good students of tuberculosis who will maintain their interest over a long period. A consideration of the promising subjects for study may be offered, if only to suggest the magnitude of our need. The first and ever-present topic in the minds of all is the search for a curative substance or method of treatment. I need hardly remark that the slightest hope of success would justify the investment of millions; but to obtain such substantial aid no promise can be made based on present knowledge. The comment might be advanced, however, that much money is wasted in commercial ventures with less prospect of return.

Without lessening the expenditures now made on the care of the tuberculous sick there is every reason to enter upon a more earnest effort in large scale experimental research toward the goal that has the greatest appeal. It is hard for the uninitiated to realize that all our present activities are aimed at the prevention and cure of tuberculosis, though to them we are following up unimportant side issues in our technical publications.

They should be told that we are paving the way and only attempting the research within our means. Moreover, vastly more knowledge may be required of physiology, chemistry and pathology, as related to tuber-

[2] An excellent plea has recently been made by Dr. S. J. Maher, Chairman, State Tuberculosis Commission, Connecticut, *Boston Medical and Surgical Journal*, November 29, 1923.

culosis, before a direct attack on the bacillus would be successful. There are very nebulous ideas prevailing about the nature of tuberculosis among many physicians and laymen that result in suggestions, serious and urgent, to try this and that cure in fruitless experiments.

Much time and money can be wasted in this way and the National Tuberculosis Association will do well to avoid devoting its resources for such uses. There is little risk that a valuable idea will be turned down under such circumstances.

There are very many chemical compounds yet to be made and tried that require close coöperation between expert chemists and bacteriologists for an orderly research in chemotherapy.

It is perfectly reasonable to conceive of an agent being discovered that may be capable of preventing the spread of tuberculosis in the body, and thus leading to an arrest if not the cure of the disease. Many other studies must go hand in hand, both clinical and laboratory, to make a successful attack on the main problem.

Just at present the subject of radiant energy in light, heat and X-rays calls for thorough investigation. There is much interest in the growth-producing vitamines, the internal secretions and the general subject of nutrition, which we are bound to consider of importance in the development of the disease from latent infection.

All of these problems relate to prevention and cure, to resistance and immunity. They interlock, and undoubtedly are beyond the power of any single individual to solve unaided.

The sciences are, of necessity, subdivided and have to be coördinated: so, it appears to me, must tuberculosis research be handled, whatever plan the National Tuberculosis Association may adopt in the future. Such an achievement would be greatly facilitated by securing the assistance of the large foundations to which some special work could be assigned. Not that it should remain an exclusive field for them, but that the varied resources and talents of the nation should recognize their privilege and duty to contribute liberally to the common cause.

Furthermore, the large insurance companies, the great industries, and especially those dealing with food products, have abundant reason to join in such a concerted scientific attack on tuberculosis. Whether any organization of the character of the National Tuberculosis Association could accomplish it or not, it can promote it.

It is not too much to hope and expect that an institute might be established where, under one roof, a group of workers could be gathered

together and continually engaged in study and investigation. Their support should be sufficient to make it a suitable career to offer to trained men and women. In this way also, I believe, trained workers can be provided who will go forth to other institutions where they can best continue their studies in any special subject, equipped and prepared for great usefulness. In order to accomplish this object, and to assure the stability of the project, I would propose a plan by which the money could be provided.

This Association began with a name suggesting the definite objects of the "Study and Prevention" of tuberculosis. It was so intended and it has never lost sight of these. Possibly but for the war more attention would have been given to subsidizing studies in addition to the important educational work and the promotion of dispensaries, sanatoria and hospitals.

The present condition of the country is more favorable for fundamental research, according to the original purpose of the founders of this body. With a special finance committee or treasurer, funds could be set aside each year, as an endowment for research. Gifts and legacies could be received and invested, the income of which might be available for a variety of purposes and should be as unrestricted as possible. This will immediately serve to keep alive, and much more active, interest and a permanent policy; and, as the latter became recognized and established, it would of itself, greatly encourage workers. Prizes might be added as a stimulus, yet in my opinion they have less value in producing the best workers.

The challenge lies at the feet of America, with Europe impoverished and impotent to carry on the very work which was so fruitful in her hands before the war.

It must rest with the genius of America and the American spirit of independent thought to prove itself equal to the task, so well conceived in the work of this Association.

END RESULTS OF 600 CASES OF PULMONARY TUBERCULOSIS TREATED BY ARTIFICIAL PNEUMOTHORAX[1, 2]

RAY W. MATSON, RALPH C. MATSON AND MARR BISAILLON

The material observed in this study consists of 600 cases of pulmonary tuberculosis, mostly of the advanced type, which were subjected to artificial-pneumothorax treatment during a period of twelve years ending January 1, 1923. It has involved over 12,000 inflations.

Drawing conclusions from a study of any large series of cases that covers a long period of years is handicapped by the difficulty of accumulating accurate information regarding the present status of many cases. Realizing the notorious unreliability of statistics and wishing to reduce to a minimum any error in data led us at the very beginning of our work to accumulate information regarding all patients subjected to pneumothorax treatment.

Our work has been greatly facilitated because of the fact that most cases included in our series were permanent residents of the Pacific Northwest and not of the migratory consumptive class.

Pneumothorax cases are never discharged from observation. In keeping with this policy, we have kept in contact with most of our living cases by periodic reëxaminations and, when this was impossible, by correspondence. Many cases completed ten years ago still submit themselves to an annual or biennual reëxamination.

In order to complete our records, we sent questionnaires to all patients in this series concerning whom there was doubt regarding their present status, and when no replies were received their condition was classified according to their last report, but none of them was given a better rating than *favorably influenced*, irrespective of how much the last report justified a better one. Cases in which the period of treatment or observation was so brief that reliable conclusions were impossible were excluded. No case has been classified *clinically well* (*apparently cured*) that received treatment later than January, 1921. Irrespective of how appar-

[1] From the Portland Open Air Sanatorium, Portland, Oregon.

[2] Read in part at the Nineteenth Annual Meeting of the National Tuberculosis Association, Santa Barbara, California, June 20–23, 1923.

ently clinically well at this time, they have been recorded as *arrested.* No case has been considered *clinically well* (*apparently cured*) unless it conformed to the requirements of the National Tuberculosis Association.

In our final analysis we again reviewed in detail all records pertaining to each case, including the reëxamination of approximately 5,000 X-ray plates and orthodiagrams. We feel, therefore, that these statistics are as accurate as it is possible for us to present.

CONTROL OF PNEUMOTHORAX CASES

Realizing the great importance of sanatorium education and observation, we have not accepted any patient for pneumothorax treatment who was unwilling to submit to an initial period of sanatorium care. All patients received their early pneumothorax treatment in the Portland Open Air Sanatorium.

They were not subjected to artificial-pneumothorax treatment until after a reasonable trial of the usual sanatorium methods, unless they were of a character that justified the assumption that a cure would not be effected by the usual treatment. Pleuritis-with-effusion cases (Clinical group 5) were the only exception to this rule. These were treated by aspiration and replacement with air, for reasons given in the discussion of that clinical group.

Aside from the pleuritis-with-effusion cases, there were, quite naturally, others subjected to pneumothorax who would have no doubt recovered without it. However, our conservatism in selecting patients for artificial pneumothorax is attested by the fact that there were only 5 per cent of recoveries and 65 per cent of deaths in cases in which pleuritic adhesions prevented pneumothorax treatment, whereas in cases in which a satisfactory collapse was accomplished 48 per cent are clinically well and 22 per cent are dead.

The period of sanatorium treatment: This was reduced to the minimum compatible with safety, patients being discharged to ambulant care as soon as possible.

The period of sanatorium treatment of pneumothorax cases is shown in table 1, but cases in which a pneumothorax could not be established because of no free pleural space are not included in the following table for the reason that they received no actual pneumothorax treatment.

Before patients were permitted to receive ambulatory treatment they remained in the sanatorium until, under a system of regulated

TABLE 1
PERIOD OF SANATORIUM TREATMENT OF 480 COLLAPSED CASES

LESS THAN 3 MO.	3 TO 6 MO.	6 MO. TO 1 YR.	OVER 1 YR.
212	178	78	12

TABLE 2
DURATION OF PNEUMOTHORAX TREATMENT OF 480 COLLAPSED CASES

PNEUMOTHORAX CHARACTER	LESS THAN 6 MO.	LESS THAN 1 YR.	OVER 1 YR.[1]
SATISFACTORY	27 %	14 %	59 %
PARTIAL	60 %	27 %	13 %

1. MANY OF THESE CASES HAVE BEEN UNDER TREATMENT OVER FIVE YEARS.

TABLE 3
DURATION OF OBSERVATION OF 600 CASES OF PULMONARY TUBERCULOSIS TREATED BY ARTIFICIAL PNEUMOTHORAX

PNEUMOTHORAX CHARACTER	LESS THAN 1 YR.	1 TO 2 YRS.	OVER 2 YRS.[1]
SATISFACTORY	29 %	24 %	47 %
PARTIAL	60 %	25 %	15 %
NO FREE SPACE	58 %	23 %	19 %

1 MANY OF THESE CASES HAVE BEEN UNDER OBSERVATION OVER FIVE YEARS.

activities, we were convinced that they were able to report for reinflations without untoward results.

Ambulant treatment and observation in every case were carried on as long as possible, at times under the most unfavorable circumstances, as many patients were obliged to journey from remote points in the Pacific Northwest for reinflation. In addition, the vast majority of cases were compelled to resume occupational activities early, because of limited circumstances. However, it is not always necessary for patients to be forbidden all occupational activities while under pneumothorax treatment. As a matter of fact, nearly all of our pneumothorax patients who are being treated while ambulant are engaged in some sort of gainful occupation. Nevertheless, patients are advised not to engage in work which involves physical strain. It is striking to observe the extensive activities a patient can engage in at times without apparent harm. We have in mind a railroad surveyor who was under compression five and a half years, and during the last four and a half years of his pneumothorax treatment he performed full field duty at his occupation and is to-day clinically well.

Duration of pneumothorax treatment and observation: It has been our policy to continue pneumothorax treatment as long as possible and, while the most favorable results are associated with a satisfactory collapse over a prolonged period, we have, nevertheless, seen good results in cases in which the period of treatment was relatively short. Table 2 shows the duration of pneumothorax treatment of the collapsed cases and table 3 shows the total duration of observation of all cases comprising this study.

Aside from the pneumothorax, the "no free pleural space" cases received the same treatment as the collapsed cases. Therefore, they serve as splendid controls and are included in table 3.

CLASSIFICATION AND DESCRIPTION OF CLINICAL MATERIAL

According to the National Tuberculosis Association classification, our 600 cases comprised 85 moderately advanced cases and 515 far advanced cases. No cases with *minimal* (*incipient*) lesions were subjected to artificial pneumothorax. To make our statistics of therapeutic results more valuable, we have classified our cases into the following eight clinicopathological groups:

Clinical group 1, fibrocaseous tuberculosis: This group comprised 194 cases of fibrocaseous tuberculosis, progressive in character, in which

little or no excavation was demonstrable. Of these, 65 were moderately advanced and 129 were far advanced. The status of the noncollapsed lung in this group was as follows:

Essentially negative	Deep peribronchial infiltration	Disseminated bronchogenic caseous extension	Active fibrocaseous infiltration	Quiescent fibrocaseous infiltration
62 cases	49 cases	12 cases	50 cases	21 cases

Clinical group 2, fibrocaseous cavernous tuberculosis: This group comprised 177 cases of advanced fibrocaseous cavernous tuberculosis, all of which had cavities, demonstrable by physical diagnostic or roentgenological procedures. These cases were more advanced than those of the preceding group. The status of the noncollapsed lung in this group was as follows:

Essentially negative	Deep peribronchial infiltration	Disseminated bronchogenic caseous extension	Active fibrocaseous infiltration	Quiescent fibrocaseous infiltration
25 cases	41 cases	17 cases	70 cases	24 cases

Clinical group 3, fibrocaseous cavernous tuberculosis with cavity manifestations in foreground: This group comprised 52 cases in which the cavity manifestations were in the foreground, enormous excavation of lung tissue having taken place, leaving cavities so large that one could not hope for closure by ordinary cicatricial contractions. These cases were still more advanced than those of the preceding groups. The status of the noncollapsed lung in this group was as follows:

Essentially negative	Deep peribronchial infiltration	Disseminated bronchogenic caseous extension	Active fibrocaseous infiltration	Quiescent fibrocaseous infiltration
10 cases	13 cases	11 cases	14 cases	4 cases

In this clinical group, the extent of the physical findings is entirely out of proportion to the constitutional disturbance. In 48 per cent the average range of temperature varied between 99° and 100°F., and in 13 per cent it was 101°F. or more. In 50 per cent there was a daily average of more than 40 cc. of sputum in twenty-four hours. Most cases were of a slowly progressive type, pursuing a lingering course. Anatomically, there was a predominance of proliferative changes, the caseation and softening phases of the disease having been passed through long before.

Clinical group 4, severe acute infiltrating types of tuberculosis; caseous pneumonic and caseous bronchopneumonic forms: This group comprised 39 cases of the exudative type of tuberculosis, all of which were of a very acute, rapidly advancing type of disease, characterized by extensive invasion and associated with a violent symptom complex. The status of the noncompressed lung was as follows:

Essentially negative	Deep peribronchial infiltration	Disseminated bronchogenic caseous extension	Active fibrocaseous infiltration	Quiescent fibrocaseous infiltrations
15 cases	2 cases	8 cases	10 cases	4 cases

As contrasted with the preceding clinical group, 70 per cent of the cases in this group had an average afternoon temperature of over 101°F.

Clinical group 5, tuberculous pleuritis with effusion: In this group, we have included 20 cases of exudative pleurisy in which the clinical history and physical and roentgenological examinations clearly indicated an unquestionably tuberculous involvement of the underlying lung parenchyma. We withheld all cases of the simple exudative variety of pleurisy from pneumothorax treatment. But because of the undoubted tuberculous origin of these cases, they were treated by aspiration of the exudate and its replacement with air. This procedure lessens the danger of exudate organization and subsequent formation of dense pleuritic adhesions.

Clinical group 6, severe and uncontrollable hemoptysis: In this group we have placed 4 cases in which a pneumothorax was necessitated primarily because of severe and uncontrollable bleeding. Our records show that 75 cases had hemoptysis shortly before or immediately preceding treatment. In many cases the bleeding was severe, but we were able to classify the pathological changes in all cases, except in the four included in this group, whose critical condition precluded thorough examination, and the bleeding demanded a pneumothorax at once.

Clinical group 7, bilateral fibrocaseous cavernous tuberculosis: In our classification of the status of the contralateral lung, we have provided for all types of pathological change except that associated with the presence of demonstrable cavities. In this group, we have, therefore, placed 30 cases which presented detectable cavities in both lungs.

There was a well-founded reason for instituting a pneumothorax in all clinical group 7 cases because of the possibility that a successful collapse of the more diseased side would offer the patient a better chance

for improvement or recovery. Great caution was exercised in the selection of material in this group, and in each case the pneumothorax was delayed until activity in the opposite lung had largely subsided, leaving mostly only the presence of the cavity to fear. Of course, there was always the danger of exacerbating the disease in the non-collapsed lung, but the pneumothorax was carried on with this danger constantly in mind.

Clinical group 8, desolate bilateral or "ultimum refugium" cases: In this group we have placed 84 desolate and hopeless cases, in which a pneumothorax was instituted purely as a palliative procedure. In these cases a pneumothorax was not performed with the idea of accomplishing a cure but rather for the purpose of controlling severe symptoms and prolonging life.

CLASSIFICATION AND DESCRIPTION OF THE CONTRALATERAL LUNG STATUS

Any critical analysis of pneumothorax material must take into serious consideration the status of the contralateral lung, if one is to arrive at accurate conclusions regarding end results, as most cases subjected to treatment have more or less involvement of the opposite side. A classification of the contralateral lung changes is important, if one wishes to compare the end results of pneumothorax therapy, in the presence of an essentially negative opposite lung, with others showing various types of disease. It is also desirable on account of the fact that many observers contend that a pneumothorax is contraindicated in cases presenting more than minimal traces of tuberculosis in the non-collapsed lung.

While we realize that many types of pathological process may co-exist in the opposite lung, for statistical purposes we have selected the dominant types which we have classified as follows:

1. Essentially negative: This group comprised 128 cases in which the opposite lung revealed no demonstrable foci either by physical diagnostic or roentgenological procedures.

2. Deep peribronchial infiltration: This group comprised 113 cases. An accepted standard for the diagnosis of deep peribronchial tuberculosis has not been fixed. However, we have included in this group only those cases in which the contralateral lung presented roentgenologically a well-defined marked increase in the shadows of the hilum and parts of the bronchial tree, especially heavy markings radiating upward and

outward, well toward the superficies of the lung. Findings of this character justify the diagnosis of deep peribronchial infiltration when there is active disease on the other side.

3. Disseminated bronchogenic caseous extensions: This group comprised 48 cases in which infection of the contralateral lung took place as a result of the aspiration of bacilli-laden sputum. This is a type of lesion which is so frequent and characteristic in a study of gross pathology. These lesions are characterized by the presence of localized caseous pneumonic, caseous bronchopneumonic, or disseminated confluent tuberculous infiltrations in the perihilar regions or dependent portions of the lung parenchyma. If the lesions are deep-seated, they may escape physical diagnostic recognition but be demonstrable roentgenologically. When the superficies of the lung is invaded, they are readily recognized by physical diagnostic methods.

Roentgenologically, this type of extension is characterized by the presence of areas of increased density, corresponding to the distribution of the lesions and variable in character, according to the activity or inactivity of the process. In the diagnosis of bronchogenic extensions, there is frequently a striking disproportion between physical signs and roentgenological findings.

4. Active fibrocaseous infiltration; and 5. Quiescent fibrocaseous infiltration: These two types of contralateral lung invasion presented well-defined characteristic physical diagnostic and roentgenological findings associated with a fibrocaseous infiltration, the activity or inactivity of the process being judged by the accepted standards. Of our 600 cases, 144 had active fibrocaseous infiltration and 53 had quiescent fibrocaseous infiltration in the noncollapsed lung.

CLASSIFICATION OF PNEUMOTHORAX CHARACTER

The end results of pneumothorax therapy are so intimately associated with the character of the pneumothorax that our statistics are tabulated accordingly. Our classification of the pneumothorax character is as follows:

Satisfactory collapse: This means that a sufficient degree of collapse or compression of diseased lung tissue was produced, which, according to our experience, if maintained, would render the diseased lung, as a source of any symptom, improbable. We refer particularly to such symptoms as persistence of germ-laden sputum in quantities amounting to

20 or 30 cc. or more daily, fever of 100° or more, and tuberculo-toxemia extending over a period of two or three months after beginning pneumothorax treatment.

In former publications, we have used the term *satisfactory compression* in the same sense as we now use *satisfactory collapse.* Although satisfactory compression was used in a clinical sense and not an anatomical one, we prefer the term *satisfactory collapse.* From the beginning of our work, we have maintained the minimum degree of collapse or compression necessary to accomplish satisfactory clinical results. In most cases this amounted to a *pneumothorax of rest,* but in some instances actual compression of lung tissue was necessary to secure desired results. Nevertheless, if satisfactory results were obtained, the pneumothorax was classified as a satisfactory collapse.

Partial collapse: This term means that a satisfactory collapse or compression was unattainable, adhesions being our greatest obstacle. Thus, even though an almost total collapse or compression of the lung was produced, if we were unable thereby to establish a satisfactory pneumothorax, or to close cavities because of adhesions, the case was placed in the partial-collapse group, for the obvious reason that the character of the pneumothorax was not satisfactory.

No free space: No explanation is necessary regarding this term, except that no case has been placed in this class until repeated attempts over all lobes of the lung proved the absence of free pleural space.

Of the 600 cases selected for artificial pneumothorax, we obtained a satisfactory collapse in 235. In 245 we obtained a partial collapse, and in 120, after repeated attempts, we encountered no free pleural space.

Inflation was attempted or carried out on the right side in 300 cases and on the left side in 286 cases, and in 14 cases the pneumothorax was bilateral.

COMPLICATIONS

Complications independent of pneumothorax treatment will not be discussed in this paper, our remarks being confined to serious tuberculous complications existing before treatment and having a direct bearing on the therapeutic results, and those intrinsic to treatment.

Table 4 is a summary of the complications in the satisfactory and partial-collapse cases in each clinical group. It will be noted that very few cases are recorded as having developed tuberculous laryngitis,

tuberculous enteritis, and extension or progression of disease in the contralateral lung during treatment.

It must be emphasized that complications recorded as developing under treatment apply only to those which developed during the actual

TABLE 4

TUBERCULOUS COMPLICATIONS PRESENT BEFORE TREATMENT AND TUBERCULOUS COMPLICATIONS DEVELOPING UNDER TREATMENT AND INTRINSIC TO THE TREATMENT IN 480 COLLAPSED CASES.

CLINICAL GROUPS	LEGEND: S. SATISFACTORY COLLAPSE P. PARTIAL — TYPES OF TUBERCULOSIS	TOTAL CASES	NUMBER COLLAPSED: CASES	CHARACTER OF PNEUMOTHORAX	N.T.A. CLASSIFICATION II	N.T.A. CLASSIFICATION III	COMPLICATIONS BEFORE TREATMENT: LARYNGITIS	COMPLICATIONS BEFORE TREATMENT: ENTERITIS	COMPLICATIONS BEFORE TREATMENT: SEVERE HEMOPTYSIS	COMPLICATIONS DEVELOPING UNDER TREATMENT (1): SEROUS EXUDATE	TUBERCULOUS EMPYEMA	PROGRESSION OF DISEASE, OPP. SIDE	EARLY OBLITERATIVE PNEUMOTHORAX	PLEURAL SHOCK AND GAS EMBOLISM	SPONTANEOUS PNEUMOTHORAX	HEMOPTYSIS	ENTERITIS	PLEURISY EFFUSION, OPP. SIDE	EXTENSION OF DISEASE, OPP. SIDE	LARYNGITIS
1	FIBRO-CASEOUS PROGRESSIVE (LITTLE OR NO EXCAVATION)	134	39	S	41	58	14	6	18	17	9	4	1	1	4	0	2	0	2	0
			62	P	17	45	8	7	9	8	11	8	5	4	2	0	0	2	0	0
2	FIBRO-CASEOUS CAVERNOUS PROGRESSIVE	177	71	S	0	71	11	9	12	11	5	3	4	0	0	0	2	1	2	1
			70	P	0	70	20	13	7	14	7	9	4	2	3	5	3	3	0	0
3	FIBRO-CASEOUS CAVERNOUS CAVITY MANIFESTATIONS IN PARENCHYMA	52	21	S	0	21	6	5	0	3	6	1	1	1	0	0	0	0	0	0
			22	P	0	22	7	2	2	6	4	0	4	2	0	0	0	0	0	0
4	SEVERE ACUTE INFILTRATING CASEOUS PNEUMONIC, ETC.	33	13	S	0	13	1	3	2	4	5	1	0	1	0	0	0	1	0	0
			17	P	0	17	3	3	2	7	2	4	1	2	2	0	0	0	0	0
5	TUBERCULOUS PLEURITIS WITH EFFUSION	20	15	S	15	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			5	P	3	2	0	0	0	0	1	0	0	0	1	0	0	0	0	0
6	SEVERE AND UNCONTROLLABLE HEMOPTYSIS	4	2	S	2	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0
			1	P	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0
7	BILATERAL FIBRO-CASEOUS CAVERNOUS	30	7	S	0	7	3	1	1	2	3	1	0	0	1	1	1	0	0	0
			12	P	0	12	3	2	2	4	1	2	1	0	1	1	0	0	0	0
8	DESOLATE BILATERAL (ULTIMUM REFUGIUM)	84	7	S	0	7	1	1	4	1	1	1	0	0	0	1	0	0	0	0
			56	P	0	56	17	18	4	6	4	0	0	0	2	2	0	0	0	0
	GRAND TOTAL	600	480		78	402	94	70	66	83	53	34	21	13	16	10	8	7	4	1

1. 29 CASES HAD OTHER MISCELLANEOUS TUBERCULOUS COMPLICATIONS NOT DEPENDENT UPON TREATMENT.
2. 9 ADDITIONAL CASES OCCURRED IN "NO FREE SPACE CASES" WHILE ATTEMPTING PNEUMOTHORAX.

period of pneumothorax treatment. We therefore have not recorded those cases which developed complications after pneumothorax treatment was discontinued. This applies particularly to those cases which were favorably influenced, temporarily improved or unimproved and

those in which treatment was abandoned. Many of these already had a tuberculous laryngitis or enteritis, and in others the period of pneumothorax treatment was so short that these complications had scarcely time to develop. Many cases undoubtedly developed a terminal progression or extension of disease after suspension of pneumothorax treatment but they have also been excluded.

Since the no-free-pleural-space cases received no compression, no complications are recorded as having developed under pneumothorax treatment except pleural shock and gas embolism.

Tuberculous laryngitis, enteritis and other tuberculous complications: In spite of the fact that 94 cases had a well-defined tuberculous laryngitis before treatment, only one case developed laryngitis under treatment and compelled us to abandon the pneumothorax. According to our experience tuberculous laryngitis does not contraindicate pneumothorax treatment unless its severity interferes with the patient's nutrition. On the contrary, improvement takes place along with improvement of the lung and is often dependent upon it.

Tuberculous enteritis: This is a serious complication, and when so severe as to interfere with the proper nutrition of the patient a pneumothorax is seldom justified.

We appreciate the fact that nearly all cases of open pulmonary tuberculosis have an infiltration of the lymph follicles of the intestine which may not be productive of symptoms, but 70 of our collapsed cases presented a well-defined symptom complex of tuberculous enteritis, and its presence was confirmed by physical diagnostic or roentgenological methods. In 17 of our collapsed cases its progression caused us to abandon pneumothorax treatment. In 7 of these the complication appeared after beginning pneumothorax treatment.

Gas embolism and pleural shock: The diversity of opinion regarding the question of gas embolism and pleural shock has made it impossible for us to decide which condition occurred in some of our cases. The symptom complex of gas embolism and so called pleural shock is so similar that at the time of its occurrence it is sometimes difficult to determine with which of these conditions one has to deal, particularly in cases in which gas has been introduced or the lung parenchyma has been penetrated.

In over 12,000 inflations we have had 4 cases presenting the symptom complex usually attributed to gas embolism, two of which were fatal. We have observed the symptom complex usually attributed to pleural

shock in 15 cases, none of which was fatal. Pleural shock is of all degrees of severity. In some of our cases the symptom complex was so alarming that we felt that death was imminent.

Our experience with pleural shock or gas embolism has made us feel that they are the most dreaded of all complications arising during the course of pneumothorax treatment. All of our cases of pleural shock and gas embolism occurred in patients in whom we had to deal with adhesions. Three cases, however, had a satisfactory collapse, but ten had a partial collapse and six had no free pleural space.

Pleural shock may occur at any time during the operative procedure. In some of our cases it occurred during anesthesia infiltration of the pleura, no gas having been administered. In others it occurred during inflation and in still others it occurred during withdrawal of the inflation cannula after gas had been administered.

In some instances pleural shock developed suddenly without any warning, but in many cases it was preceded by a prodromal state which was highly suggestive. Anesthesia infiltration preliminary to an artificial pneumothorax is usually absolutely painless, but we have observed a marked hyperalgesia and hyperesthesia on the pneumothorax side in some patients who subsequently developed pleural shock. These patients were extremely hypersensitive to the preliminary anesthesia infiltration, complaining bitterly of pain not only in the skin and the infiltrated area but throughout the entire side of the chest.

The earliest symptoms of pleural shock are usually manifested in the facial expression, particularly the eyes, which are fixed sometimes in a deviated position. At times there takes place a sudden muscular movement of the patient who, upon being admonished to remain quiet, makes no reply. A hasty examination will reveal that the patient is already in pleural shock and either unconscious or, if conscious, unable to talk or control his movements, which are due to tonic and clonic muscular spasm. Many of these cases are of the convulsive type and very much resemble an epileptic seizure.

In order to detect the very earliest manifestations of pleural shock, our patients are always placed in the most comfortable position and requested not to make any sudden movement. The face is kept in full view and the eyes are carefully watched for any suggestive symptoms. Attention to these precautions may enable one to administer early treatment and sometimes avoid serious consequences.

A careful study of all our cases of pleural shock and gas embolism has been made, copious notes having been taken during the actual occurrence of the phenomena; but a review of the clinical bedside notes reveals the fact that there is no uniformity of symptoms by which we can sharply differentiate between pleural shock and gas embolism at the time of the accident.

To avoid pleural shock, apprehensive or hypersensitive patients should be mentally prepared and during the inflation one should be constantly on the alert. In individuals of this character, we have seen the symptom complex closely similar to that of pleural shock occurring in various degrees of severity at the time of each reinflation, which, along with other stigmata, convinced us that it was purely hysterical.

After a fatality from gas embolism occurring during inflation, adhesion cases are approached with much timidity. One hesitates to introduce gas in a case showing a slight manometer excursion, indicating an adherent pleura; and yet one is tempted to, because of the feeling that the needle outlet is resting between the pleural surfaces and that they may separate, as they often do, following gas introduction. However, in these cases, it has been our custom to attempt separation of the pleural surfaces by introducing normal salt solution through the pneumothorax needle. The introduction of salt solution for the purpose of finding free pleural space is free from the danger of gas embolism; and frequently the pleural surfaces separate, permitting subsequent gas introduction. In case inadequate free space is produced to justify even a partial collapse, we frequently introduce hypertonic salt solution (2.5 to 10 per cent) into pockets between the pleural surfaces. This causes an inflammatory reaction, the severity of which can be regulated by the strength of the salt solution; and, subsequently, proliferative inflammatory changes take place, followed by marked pleuritic thickening and, still later, retraction. This serves to lessen respiratory movement and rests the diseased side. We feel that this method is of value, not only in avoiding gas embolism but also as a therapeutic procedure in cases in which adhesions prevent establishing a pneumothorax. We have never had a gas-embolism or pleural-shock symptom complex occur when we followed this procedure. We have used the method also to produce retraction changes prior to thoracoplastic operations.

Serous exudate: Of our 480 collapsed cases, 83 developed a serous exudate in amounts of 50 cc. or more. We believe that nearly all cases develop an exudate at some time during their pneumothorax treatment,

if the pneumothorax is maintained long enough; but the quantity may be so small as to escape recognition, unless specially sought. The exudate may fill only a portion of the phrenicocostal sinus, it may be transitory in character, lasting but a few days, and it may be productive of no clinical symptoms. Serous exudates may follow the separation of adhesions, but we doubt whether this is the usual cause. The mere presence of gas in the pleural cavity acting as a foreign body and the unphysiological intrapleural pressure conditions are sufficient to produce an exudate.

Tuberculous empyema: There were 59 cases (12 per cent) of tuberculous empyema in our 480 collapsed cases. This number included some patients who presented themselves with a tuberculous empyema associated with a spontaneous pneumothorax and also included all those cases which early in our work we designated as *sterile empyema.*

Our observations during recent years have convinced us that nearly all purulent exudates complicating artificial pneumothorax are tuberculous in character and we have been able to demonstrate this by animal inoculation. Tuberculous empyema usually arises from ulceration of a superficial caseated focus into the pneumothorax cavity or as a result of spontaneous pneumothorax. Tearing a portion of the lung cortex, and thus exposing tuberculous foci while separating adhesions, is also a cause in some cases.

In our series of 59 cases, empyema was just as frequent in the partial-collapse cases, in which adhesions were necessarily under tension, as in the satisfactory-collapse cases, in which they were not necessarily so (12 per cent of each).

Empyema occurred in each clinical group very much in proportion to the duration of the pneumothorax and the intensity of the disease. The longer the pneumothorax was maintained and the more widespread the disease, the more frequently empyema was a complication. It naturally follows that the longer the pleural surfaces are separated and the more progressive and widespread the disease, the greater the opportunity for infection of the pleural cavity by the breaking down of tuberculous foci. Contrariwise, if the pleural surfaces are in contact, protective adhesions form and prevent infection of the pleural cavity, except, of course, in those cases in which spontaneous rupture of a superficial cavity takes place following physical exertion or coughing, sneezing, etc.

It is important to aspirate a tuberculous empyema early and often, supplemented by irrigation with normal or hypertonic salt solution, if

necessary, in an effort to affect its early permanent disappearance, for the reason that the prolonged presence of the empyema enhances the danger of lung perforation. We feel that, in at least two of our cases, lung perforation would have been avoided by early aspiration. In both of these the exudate produced only minor clinical symptoms and for this reason was allowed to remain undisturbed. In cases failing to clear up by aspiration, or aspiration and irrigation with normal salt solution, we have employed hypertonic salt solution with advantage. After aspiration we inject an amount of hypertonic salt solution equal to about half the volume of aspirated fluid, using first a 2 per cent solution, and increasing it according to the indications to even a 10 per cent solution. The stronger solutions are used in stubborn cases for the purpose of setting up proliferative changes and converting the pneumothorax into an obliterative pneumothorax in preference to establishing tube drainage.

Tube drainage should never be resorted to unless all other measures fail; and, in case of this necessity, the drainage should be airtight and an effort made to expand the lung as quickly as possible. Of our 59 cases of tuberculous empyema, we resorted to airtight tube drainage with constant suction under slight negative pressure in 5 cases, with two complete recoveries and three deaths. Three other cases that developed an empyema while away from our observation were operated upon by the ordinary open method and died. Three additional cases were also operated upon by surgeons by the open method and are still living but will require radical thorocoplastic procedures to obliterate their pneumothorax cavities.

Spontaneous pneumothorax: In our series of 480 collapsed cases, 16 (approximately 3 per cent) developed a spontaneous pneumothorax into the pneumothorax cavity and it was fatal in 3 cases. Spontaneous pneumothorax or lung perforation into the pneumothorax cavity occurs with greater frequency than is generally recognized, for the reason that some cases are not productive of symptoms and in others the symptoms are so mild that they are attributed to other causes.

The perforation may be so small as to permit only a slow leakage of air and may not cause any subjective symptoms. At times, the only absolute evidence of perforation is obtained from the manometric readings. The symptoms are largely dependent upon the size of the pneumothorax cavity, the presence or absence of adhesions or exudate and the size and character of the perforation, that is, whether of the valve type or not.

Although our series of lung perforations is small and justifies no conclusions, we feel, as in the case of empyema, that the most frequent cause of perforation is the breaking down of tuberculous foci in the lung cortex.

While 10 of our 16 cases occurred in partial-collapse cases, in which stripping off of a portion of the lung cortex or tearing the wall of the cavity in separating adhesions may have been etiological factors, we are not convinced that even in these cases the perforation was not due to the ulceration of a superficial caseous focus, as in the case of empyema, or to sudden rupture of a superficial cavity.

Lung perforation may occur as a result of any condition which suddenly produces a great increase in the intrapleural pressure, particularly coughing paroxysms or physical strain. Two of our cases ruptured the lung following coughing and four during or after physical strain. Two of these occurred while straining at stool.

Irrigation of the pleural cavity in empyema is not without danger, especially if one employs a large quantity of solution, thereby raising the intrapleural pressure sufficiently to produce rupture. The same danger exists in the use of high pressure in combating adhesions or an early obliterative pneumothorax.

Lung perforation may follow puncture of the lung at the time of inflation, especially if one employs a sharp-pointed reinflation needle.

Not all cases of spontaneous pneumothorax into a pneumothorax cavity are associated with the formation of exudate. The majority, however, are soon followed by an exudate, which at first may be serous, quickly becoming turbid, and then purulent or mucopurulent.

When the rupture of a cavity into the pneumothorax cavity takes place, the patient may suddenly fail to raise the usual amount of sputum or expectoration may cease altogether, for the reason that the sputum drainage takes place into the pneumothorax cavity.

The size of the spontaneous pneumothorax will depend upon the extent and character of adhesions. Those in which adhesions permit only a localized spontaneous pneumothorax offer a much better prognosis.

Hemoptysis: Hemoptysis was present, preceding or shortly before pneumothorax treatment, in 82 cases. It developed during treatment in 10 cases. Aspiration tuberculosis, as a result of hemoptysis, developed in two cases and it was fatal in both instances.

Extension of disease to the contralateral lung: We have employed the term *extension of disease* only with reference to invasion of an essentially

negative contralateral lung during collapse of the other side, whereas the term *progression of disease* is applied to those cases in which there was an exacerbation of disease already present in the contralateral lung. Thus the former represents extension to the nondiseased contralateral lung and the latter progression in the already diseased contralateral lung. Our records show that we designated the status of the contralateral lung as essentially negative in 107 collapsed cases. Extension of disease to the contralateral lung occurred as a complication in four instances, but none was fatal.

Progression of disease in the contralateral lung: In 480 collapsed cases, 282 had demonstrable disease in the opposite lung, yet a progression of the disease took place in only 34 cases during the actual period of pneumothorax treatment. Undoubtedly, a minor progression took place in other cases, particularly early in their treatment, but the limitations of diagnostic procedures are such that it is not always possible to detect the minor or questionable degrees of progression in an already diseased area, particularly if it is deep-seated. But in the 34 cases referred to, it was of such unquestionable character that a discontinuance of pneumothorax treatment was necessitated. In 22 cases it was fatal.

The 34 instances in which progression of disease in the contralateral lung took place do not, of course, include cases in which progression of disease took place following discontinuance of the pneumothorax, such as occurred in cases in which the pneumothorax was discontinued because of a progressive enteritis or unsatisfactory collapse. Neither does it include no-free-space cases, because these cases were not under pneumothorax treatment.

Early obliterative pneumothorax: Obliterative changes develop sooner or later in all pneumothorax cases under ordinary circumstances, the time required for completion varying within a wide range. We have been successful in maintaining compression in some cases for periods in excess of six years.

A study of our records shows that out of 245 partial collapses the pneumothorax was maintained for less then six months in 149, yet even these short periods of inflation have been productive of beneficial results. These cases are not, however, designated *early obliterative pneumothorax*, because the obliterative process took place in the usual manner. However, in 21 cases, as a result of proliferative inflammatory changes with organization of exudate and dense pleuritic thickening, it took place with such unusual rapidity that we have classed them as early obliterative

pneumothorax. In two cases the tuberculous process was progressive and terminated fatally.

Pleurisy with effusion on the noncollapsed side: This interesting and unusual complication occurred seven times among out 480 collapsed cases. In one case, the noncollapsed lung had a deep peribronchial infiltration, four had active fibrocaseous infiltrations, one had a disseminated bronchogenic caseous extension and one occurred in a bilateral fibrocaseous cavernous case. In five cases there was a partial pneumothorax on the collapsed side, and in two the pneumothorax was satisfactory. This complication will be discussed in a future contribution.

Miscellaneous tuberculous complications: These occurred in 29 cases, and included several of urogenital tuberculosis, one of which was fatal, and one tuberculous meningitis which was fatal.

RESULTS OF TREATMENT

Information compiled from end-results without any consideration of expired time would be misleading and, furthermore, it would be unfair to compare the number of cases alive to-day and treated ten years ago with the number alive to-day and treated two years ago, if for no other reason than that of the natural mortality of disease in general and tuberculosis in particular. In our endeavor to eliminate these factors, we have grouped our cases into three epochs of four years each, 1911–1914, 1915–1918 and 1919–1922, inclusive. Thus we are able to compare the present status of a case treated in any one epoch with that of any other epoch.

In table 5 are shown the results of treatment in each clinical group according to the character of the pneumothorax in each of the three epochs.

In comparing the number *clinically well* in the epochs, 1915–1918 and 1919–1922, it will be seen that the number of cures in the latter epoch is considerably smaller than in the former. This is because no patient has been classified as *clinically well* in the epoch 1919–1922 who received treatment later than January 1, 1921. Irrespective of how apparently well these cases were, they have been designated *arrested*, pending the expiration of the required two-year period of freedom from all constitutional disturbance and bacilli-laden sputum. Of our 600 cases, 149, or 25 per cent, are clinically well; 84, or 14 per cent, are arrested; and 274, or 45 per cent, are dead. The remaining cases were either favorably influenced, temporarily improved or unimproved.

TABLE 5

RESULTS OF TREATMENT IN THE DIFFERENT CLINICAL TYPES OF TUBERCULOSIS AND ACCORDING TO THE CHARACTER OF THE PNEUMOTHORAX

CLINICAL GROUPS	TYPES OF TUBERCULOSIS (LEGEND: S. SATISFACTORY COLLAPSE; P. PARTIAL COLLAPSE; N. NO FREE SPACE)	TOTAL CASES	NO. OF CASES AND CHARACTER OF PNEUMOTHORAX	N.T.A. CLASSIFICATION II A	II B	II C	III A	III B	III C	RESULTS OF TREATMENT: CLINICALLY WELL 1911-14	1915-18	1919-22	%	ARRESTED AMBULANT 1911-14	1915-18	1919-22	%	PAR. INFLUENCED TEMP. IMPROVED UNIMPROVED	DEAD 1911-14	1915-18	1919-22	%
1	FIBROCASEOUS PROGRESSIVE (LITTLE OR NO EXCAVATION)	194	39 S	6	15	6	6	34	16	6	26	22	33	0	3	12	15	12	10	5	4	13	4	21
			82 P	1	12	3	4	17	24	1	4	6	17	0	3	9	12	7	18	11	5	16	8	46
			33 N	0	6	1	2	15	9	0	5	0	15	0	1	3	12	0	0	7	6	9	3	24
		TOTALS		65			129			63		39		31		15		70			68			35
2	FIBRO-CASEOUS-CAVERNOUS PROGRESSIVE	177	71 S	0	0	0	6	32	33	2	18	9	40	0	3	26	32	5	7	5	3	16	2	15
			70 P	0	0	0	9	38	31	0	6	2	11	1	0	11	17	19	11	15	11	13	6	44
			36 N	0	0	0	6	17	13	0	1	1	5	0	0	3	8	0	0	9	4	13	5	61
		TOTALS		0			177			39		22		38		21		71			63			35
3	FIBRO-CASEOUS-CAVERNOUS (CAVITY MANIFESTATIONS IN FORE-GROUND)	52	21 S	0	0	0	1	9	11	0	4	5	43	1	0	4	24	5	0	1	1	4	1	28
			23 P	0	0	0	2	8	12	0	1	2	13	0	0	2	9	5	5	4	3	7	4	63
			9 N	0	0	0	0	6	3	0	0	0	0	0	0	2	22	0	0	3	0	3	1	44
		TOTALS		0			52			12		23		9		17		23			24			46
4	SEVERE ACUTE INFILTRATING CASEOUS PNEUMONIC CASEOUS BRONCHOPNEUMONIC	39	13 S	0	0	0	0	2	11	0	2	4	46	0	0	1	7	2	1	3	0	3	0	23
			17 P	0	0	0	0	0	17	0	0	1	6	0	0	0	0	3	2	8	3	7	3	76
			9 N	0	0	0	0	1	8	0	0	0	0	0	0	0	0	0	0	1	2	1	4	97
		TOTALS		0			39			7		11		1		2		20			23			58
5	TUBERCULOUS PLEURITIS WITH EFFUSION	20	15 S	12	3	0	0	0	0	7	5	1	86	0	0	0	0	0	1	0	1	1	0	13
			5 P	1	0	2	1	1	0	1	1	2	80	0	0	0	0	0	1	0	0	0	0	0
			0 N	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		TOTALS		18			2			17		85		0		0		2			2			10
6	SEVERE AND UNCONTROLLABLE HEMOPTYIS	4	2 S	1	1	0	0	0	0	1	1	0	100	0	0	0	0	0	0	0	0	0	0	0
			1 P	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	100	0	0	0	0	0
			1 N	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	100
		TOTALS		2			2			2		50		1		25		0			1			25
7	BILATERAL FIBRO-CASEOUS CAVERNOUS	30	7 S	0	0	0	0	3	4	0	2	1	42	0	0	0	0	2	2	2	1	2	1	57
			12 P	0	0	0	0	4	8	0	0	1	8	0	1	1	16	3	0	4	2	4	1	58
			11 N	0	0	0	0	2	9	0	0	0	0	0	0	1	18	0	0	4	1	2	4	63
		TOTALS		0			30			4		13		4		13		17			18			60
8	DESOLATE BILATERAL (ULTIMUM REFUGIUM)	84	7 S	0	0	0	0	1	6	0	0	0	0	0	0	0	0	2	0	1	0	3	2	71
			54 P	0	0	0	0	9	41	0	0	0	0	0	0	0	0	5	4	34	6	33	10	87
			21 N	0	0	0	2	2	17	0	0	0	0	0	0	0	0	0	3	2	16	3	100	
		TOTALS		0			84			0		0		0		0		49			75			89
GRAND TOTAL		600		85			515			149		25%		84		14%		370	62	120	274			45%

TABLE 6

SUMMARY OF RESULTS OF TREATMENT OF FIBROCASEOUS (PROGRESSIVE WITH LITTLE OR NO EXCAVATION) TYPES OF TUBERCULOSIS, ACCORDING TO "STATUS OF CONTRALATERAL LUNG", IN COLLAPSED AND NO FREE SPACE CASES

STATUS OF CONTRALATERAL LUNG	NO. CASES	COLLAPSED CASES				NO FREE SPACE CASES			
		NO.	% CLINICALLY WELL	% ARRESTED	% DEAD	NO.	% CLINICALLY WELL	% ARRESTED	% DEAD
ESSENTIALLY NEGATIVE	62	50	56	10	14	12	33	0	66
DEEP PERIBRONCHIAL INFILTRATION	49	43	41	43	32	6	0	33	33
DISSEM. BRONCHOGENIC CASEOUS INFILTRATION	12	11	11	27	55	1	0	0	0
ACTIVE FIBROCASEOUS INFILTRATION	50	43	28	16	44	7	0	14	80
QUIESCENT FIBROCASEOUS INFILTRATION	21	14	50	21	28	7	14	14	28
TOTAL	194	161	40	16	31	33	15	12	54

Granting that the patient is willing and able to coöperate, and economic and social conditions are favorable, and there are no contra-indications in the way of complications, the three factors of greatest moment in determining the end-results of pneumothorax treatment are, in the order of their importance, (1) *type of disease*, (2) *character of pneumothorax* and (3) *status of the contralateral lung*.

In order to make our statistical elements more nearly comparable, we have noted the results of treatment in each clinical group according to the character of the pneumothorax and according to the status of the contralateral lung. However, the scope of this paper does not permit a complete presentation of all our data which are summarized as follows:

Clinical group 1, fibrocaseous tuberculosis, progressive, with little or no excavation: Of 194 cases in this group (table 5) 35 per cent are clinically well, 15 per cent are arrested and 35 per cent are dead. The remaining cases were either favorably influenced, temporarily improved or unimproved.

There were 99 satisfactory-collapse cases, of which 53 per cent are clinically well, 15 per cent are arrested and 21 per cent dead. Of 62 partial-collapse cases, 17 per cent are clinically well, 19 per cent arrested and 46 per cent dead. Of 33 no-free-space cases, 15 per cent are clinically well, 12 per cent arrested and 54 per cent dead. The best results in our entire series were obtained in this clinical group, especially in 36 cases in which the contralateral lung was essentially free from disease and a satisfactory collapse was obtained, 61 per cent of whom are clinically well, 14 per cent arrested and 11 per cent dead.

Table 6 shows the results of treatment in collapsed cases (satisfactory and partial) and no-free-space cases, in this clinical group, according to the contralateral lung status. The influence of the contralateral lung is strikingly shown in the collapsed group. In this clinical group of 194 cases, there were 62 with an essentially negative contralateral lung. Fifty of these cases were collapsed (satisfactory and partial), and 56 per cent are clinically well, 10 per cent arrested and 14 per cent dead. It will be noted that the percentage of clinically well, with various types of disease in the contralateral lung, occurs in the following order: Quiescent fibrocaseous infiltration, 50 per cent; deep peribronchial infiltration, 41 per cent; active fibrocaseous infiltration, 28 per cent; and disseminated bronchogenic caseous infiltration, 11 per cent.

Comparing the collapsed and no-free-space cases in this clinical group, it will be noted that 40 per cent of the collapsed cases are clinically well

TABLE 7

SUMMARY OF RESULTS OF TREATMENT OF FIBROCASEOUS CAVERNOUS (PROGRESSIVE) TYPES OF TUBERCULOSIS ACCORDING TO "STATUS OF CONTRALATERAL LUNG" IN COLLAPSED AND NO FREE SPACE CASES.

STATUS OF CONTRALATERAL LUNG	NO. CASES	COLLAPSED CASES				NO FREE SPACE CASES			
		NO.	% CLINICALLY WELL	% ARRESTED	% DEAD	NO.	% CLINICALLY WELL	% ARRESTED	% DEAD
ESSENTIALLY NEGATIVE	25	22	36	23	14	3	0	33	33
DEEP PERIBRONCHIAL INFILTRATION	41	30	23	30	33	11	9	0	45
DISSEM. BRONCHOGENIC CASEOUS INFILTRATION	17	14	14	28	50	3	0	0	100
ACTIVE FIBROCASEOUS INFILTRATION	70	56	26	25	26	14	0	7	78
QUIESCENT FIBROCASEOUS INFILTRATION	24	19	26	15	26	5	20	20	40
TOTAL	177	141	25	24	29	36	5	8	61

and 31 per cent dead; whereas, of the no-free-space cases, 15 per cent are clinically well and 54 per cent dead. The ratio of satisfactory-collapse, partial-collapse and no-free-space cases was approximately 3:2:1. The largest proportion of satisfactory collapses was obtained in this clinical group.

The above results suggest the advantage of artificial pneumothorax in essentially unilateral, adhesion-free cases at a time before excavation has progressed to the formation of larger cavities. That the procedure is justified in these earlier types of cases is indicated by comparing the end-results of the collapsed cases with the no-free-space cases of this group, in which, aside from the pneumothorax, the treatment was the same.

Clinical group 2, fibrocaseous cavernous tuberculosis, progressive: Of 117 cases in this group (table 5) 22 per cent are clinically well, 21 per cent arrested and 35 per cent dead. The remaining cases were favorably influenced. There were 71 satisfactory-collapse cases, of which 40 per cent are clinically well, 32 per cent arrested and 15 per cent dead. Of 70 partial-collapse cases, 11 per cent are clinically well, 17 per cent arrested and 48 per cent dead. Of 36 no-free-space cases, 5 per cent are clinically well, 8 per cent arrested and 61 per cent dead.

This clinical group gave third-best end-results. Table 7 shows the results of treatment in the collapsed cases, (satisfactory and partial) and no-free-space cases, in this clinical group, according to the contralateral lung status.

Again, one sees the advantage of essential freedom of disease in the contralateral lung and value of collapse therapy. In this group the contralateral lung was essentially negative in 25 cases; 22 were collapsed, and 36 per cent are clinically well, 23 per cent arrested and 14 per cent dead. The percentage of clinically well, with various types of contralateral lung disease, occurred in the following order: Quiescent fibrocaseous infiltration, 26 per cent; active fibrocaseous infiltration, 26 per cent; deep peribronchial infiltration, 23 per cent; disseminated bronchogenic caseous infiltration, 14 per cent.

Comparing the collapsed cases and no-free-space cases reveals that 25 per cent of the collapsed cases are clinically well and 29 per cent are dead, whereas 5 per cent of the no-free-space cases are clinically well and 61 per cent are dead.

The ratio of satisfactory-collapse, partial-collapse and no-free-space cases was approximately 2:2:1. In this group, the destructive nature

of the disease and increasing difficulty of establishing a satisfactory collapse, because of adhesions, have materially reduced the percentage of recoveries and correspondingly increased the percentage of deaths. This again emphasizes the necessity of resorting to artificial pneumothorax before destructive lesions are established, and adhesions prevent a satisfactory collapse.

Clinical group 3, fibrocaseous cavernous tuberculosis with cavity manifestations in the foreground: Of 52 cases in this group (table 5) 23 per cent are clinically well, 17 per cent are arrested and 46 per cent are dead. The remaining cases were favorably influenced. There were 21 satisfactory-collapse cases, of which 43 per cent are clinically well, 24 per cent are arrested and 28 per cent are dead. Of 22 partial-collapse cases, 13 per cent are clinically well, 9 per cent are arrested and 63 per cent are dead. Of 9 no-free-space cases, none is clinically well, 22 per cent are arrested and 44 per cent are dead.

The results of treatment in this group were slightly better than in clinical group 2. However, this group comprised mostly cases with torpid lesions, the patient having survived the destructive process and being left with more or less stationary cavities. Many of this group were chronic invalids, who had previously been subjected to the usual sanatorium regimen and change of climate and had failed to recover. Others in this group were wage-earners, living and working with others and having little constitutional disturbance; but all of these cases raised large quantities of sputum, laden with tubercle bacilli. Consequently, it is a great gain, at least from the standpoint of prophylaxis alone, to have restored some of these cases to health.

Table 8 shows the results of treatment in the collapsed cases (satisfactory and partial) and the no-free-space cases, in this group, according to the contralateral lung status.

In this group, the contralateral lung was essentially negative in 10 cases. Of these, 9 were collapsed; and 33 per cent are clinically well, 11 per cent are arrested and 44 per cent are dead. The percentage of clinically well with various types of contralateral lung lesions occurs in the following order: Quiescent fibrocaseous infiltration, 50 per cent; active fibrocaseous infiltration, 30 per cent; deep peribronchial infiltration, 22 per cent; disseminated bronchogenic caseous infiltration, 20 per cent. It will be seen that the percentage of clinically well, with quiescent fibrocaseous infiltrations in the contralateral lung, exceeded the essentially negative cases; however, in the former, there were only four cases; consequently, the difference is of no significance.

TABLE 8

SUMMARY OF RESULTS OF TREATMENT OF FIBROCASEOUS CAVERNOUS (CAVITY MANIFESTATIONS IN FOREGROUND) TYPES OF TUBERCULOSIS, ACCORDING TO "STATUS OF CONTRALATERAL LUNG," IN COLLAPSED AND NO FREE SPACE CASES.

STATUS OF CONTRALATERAL LUNG	NO. CASES	COLLAPSED CASES				NO FREE SPACE CASES			
		NO.	% CLINICALLY WELL	% ARRESTED	% DEAD	NO.	% CLINICALLY WELL	% ARREST-ED	% DEAD
ESSENTIALLY NEGATIVE	10	9	33	11	44	1	0	0	0
DEEP PERIBRONCHIAL INFILTRATION	13	9	22	22	55	4	0	25	50
DISSEM. BRONCHOGENIC CASEOUS INFILTRATION	11	11	20	20	55	0	-	-	-
ACTIVE FIBROCASEOUS INFILTRATION	14	10	30	20	40	4	0	25	50
QUIESCENT FIBROCASEOUS INFILTRATION	4	4	50	0	50	0	-	-	-
TOTAL	52	43	27	16	46	9	0	22	44

Comparing the collapsed cases and no-free-space cases shows that 27 per cent of the collapsed cases are clinically well and 46 per cent are dead, while none of the no-free-space cases is clinically well and 44 per cent are dead.

The results of the usual sanatorium treatment in this type of tuberculosis are unsatisfactory. Clinical recoveries are uncommon, although they do have prolonged periods of quiescence and even arrest. Clinically effective degrees of collapse are difficult in these cases, because of adhesions; but one sees splendid results if the cavities are not extensive or superficial. In the latter cases adhesions are invariably present, preventing satisfactory collapse. The sooner collapse therapy is instituted in these cases the better. Not only is the danger of intestinal infection diminished, but the possibility of bronchogenic caseous extension on the same side and to the other side is lessened.

The ratio of satisfactory collapse, partial collapse and no-free-space cases in this group was approximately 2 : 2 : 1.

Clinical group 4, severe acute infiltrating caseous pneumonic and caseous bronchopneumonic forms of tuberculosis: Of 39 cases in this group (table 5) 17 per cent are clinically well, 2 per cent are arrested and 58 per cent are dead. The remaining cases were favorably influenced. There were 13 satisfactory collapse cases, of which 46 per cent are clinically well, 7 per cent arrested and 23 per cent dead. Of 17 partial-collapse cases, 6 per cent are clinically well, none is arrested and 76 per cent are dead. Of 9 no-free-space cases, none is clinically well, none is arrested and 97 per cent are dead.

Thus, it will be seen that in no class of cases is a satisfactory collapse so vital as in this group. A partial collapse in these types of tuberculosis is of slight value as compared with the foregoing groups. There was only one recovery in this group under partial collapse, and that occurred in a case with an essentially negative contralateral lung. Table 9 shows the results of treatment in collapsed (satisfactory and partial) and no-free-space cases, in this group, according to the status of the contralateral lung. The essentially negative cases numbered fifteen; 11 were collapsed and of these, 3 or approximately 27 per cent are clinically well The percentage of clinically well with various types of contralateral lung lesions was as follows: Deep peribronchial infiltrations, one case, 100 per cent; disseminated bronchogenic caseous infiltration, one case, 12 per cent; active fibrocaseous infiltration, none; and quiescent fibrocaseous infiltration, two cases, 66 per cent. The number of cases in each

TABLE 9

SUMMARY OF RESULTS OF TREATMENT OF ACUTE INFILTRATING, CASEOUS PNEUMONIC AND CASEOUS BRONCHOPNEUMONIC TYPES OF TUBERCULOSIS. ACCORDING TO "STATUS OF CONTRALATERAL LUNG" IN COLLAPSED AND NO FREE SPACE CASES.

STATUS OF CONTRALATERAL LUNG	NO. CASES	COLLAPSED CASES				NO FREE SPACE CASES			
		NO.	% CLINICALLY WELL	% ARRESTED	% DEAD	NO.	% CLINICALLY WELL	% ARRESTED	% DEAD
ESSENTIALLY NEGATIVE	15	11	27	0	55	4	0	0	100
DEEP PERIBRONCHIAL INFILTRATION	2	1	100	0	0	1	0	0	100
DISSEM. BRONCHOGENIC CASEOUS INFILTRATION	8	8	12	0	37	0	-	-	-
ACTIVE FIBROCASEOUS INFILTRATION	10	7	0	14	85	3	0	0	33
QUIESCENT FIBRO CASEOUS INFILTRATION	4	3	66	0	33	1	0	0	100
TOTAL	39	30	23	3	53	9	0	0	77

contralateral-lung status is too small to permit valuable deductions, except possibly in the essentially negative class, in which 27 per cent are clinically well and 55 per cent are dead. Of 9 no-free-space cases in this clinical group, 77 per cent are dead and the remaining cases (3) are progressively declining. Some writers consider caseation a contraindication for pneumothorax. However, according to our experience, it is not. Nevertheless, extreme caution must be used in these cases, because active lesions are frequently present in the noncollapsed lung. In cases with severe toxemia and rapidly advancing disease, pneumothorax is of doubtful value. The ratio of satisfactory collapse and partial collapse to the no-free-space cases was approximately 3:3:2. Thus, it will be seen that adhesions are a greater menace in this group than in the preceding groups.

Clinical group 5, tuberculous pleuritis with effusion: There were 20 cases in this group, in which a tuberculous basis seemed unquestionable (table 5). They are treated by fluid aspiration and replacement with air, for reasons previously stated. Of the 20 cases, 17 are clinically well and 2 are dead. Both deaths were due to extraneous causes. The remaining case was temporarily improved but treatment was discontinued.

Clinical group 6, severe hemoptysis: This group comprised 4 cases of uncontrollable hemoptysis, threatening the life of the patient in each instance (table 5). Two are clinically well, one arrested and one dead. These cases, when first seen, were bleeding so profusely that the bleeding side was determined with difficulty, as careful examination was impossible and the bleeding demanded a pneumothorax at once.

Artificial pneumothorax is obligatory in these cases, because not only does it put a quick end to bleeding if a satisfactory collapse can be obtained, but it lessens the danger of aspiration pneumonia.

Of the four cases, the two clinically well had a satisfactory collapse. The arrested case had a partial collapse, and in the one fatal case no free pleural space could be found.

Clinical group 7, bilateral fibrocaseous cavernous tuberculosis: Of the 30 cases in this group (table 5) 13 per cent are clinically well, 13 per cent are arrested and 60 per cent are dead. The remaining cases were favorably influenced. There were 7 satisfactory-collapse cases, of whom 3, or 42 per cent, are clinically well. None is arrested and 57 per cent are dead. Of 12 partial-collapse cases, 8 per cent are clinically well, 16 per cent are arrested and 58 per cent are dead. Of 11 no-free-space cases, none is clinically well, 18 per cent are arrested and 63 per cent are dead.

We cannot agree with those who affirm that a pneumothorax is contraindicated in the presence of a bilateral fibrocaseous cavernous tuberculosis. While it is true that clinical recoveries in this group are not many with pneumothorax treatment, it is also true that clinical recoveries by the usual sanatorium treatment without pneumothorax are rare, although "arrests" are not infrequent. In our own series, no case without a free pleural space made a clinical recovery.

Bilateral cases are frequently confusing, especially when there is an old fibrocaseous cavernous lesion on one side and a less extensive but more progressive fibrocaseous cavernous lesion on the opposite side. Acute or rapidly progressing lesions on the noncollapsed side are likely to be made worse. Disease in the noncollapsed side should be limited to the upper lobe, and not be of an acute or progressive character, and must be carefully watched and the pneumothorax cautiously brought about.

As a matter of fact, one should not aim to collapse the lung in this class of cases; a layer of "gas" between the visceral and parietal pleura is sufficient. Meanwhile, the behavior of the noncollapsed lung can be observed.

A satisfactory collapse in this group is more difficult to obtain than in any of the preceding groups, the ratio of satisfactory collapse and partial collapse to no free space being approximately 1:2:2.

Clinical group 8, desolate bilateral cases: This group comprised the 84 cases in which a pneumothorax was established as a palliative measure only. Of the 84 cases, none is clinically well, none is arrested and 89 per cent are dead. Of the remaining cases, 8 per cent were favorably influenced, 5 per cent were temporarily improved and 45 per cent were unimproved. This is admittedly not a very encouraging record. At the same time, we do not agree with those who maintain that artificial pneumothorax as a palliative measure is unjustifiable because it might bring the method into disrepute. This objection can be overcome by making it perfectly clear to the patient or the family that the method is suggested as a palliative procedure only. Furthermore, artificial pneumothorax has given relief from troublesome coughing and hemoptysis in these cases and has prolonged life which, after all, is humanitarian. At the same time, according to our present views, artificial pneumothorax is justified in but few of these cases. Its benefits are slight and never lasting. Adhesions render it almost impossible to establish a satisfactory collapse in these cases. The ratio of satisfactory-collapse, partial-collapse and no-free-space cases was approximately 1:8:3.

TABLE 10

SUMMARY OF RESULTS OF TREATMENT AND THE CHARACTER OF THE PNEUMOTHORAX

RESULT OF TREATMENT	NO. CASES	SATISFACTORY COLLAPSE		PARTIAL COLLAPSE		NO FREE SPACE	
		NO.	%	NO.	%	NO.	%
CLINICALLY WELL	149	114	76	28	12	7	4
ARRESTED	84	44	52	29	34	11	13
DEAD	274	52	15	142	52	80	29

TABLE 11

SUMMARY OF THE CHARACTER OF THE PNEUMOTHORAX AND RESULTS OF TREATMENT

CHARACTER OF PNEUMOTHORAX	TOTAL CASES	CLINICALLY WELL		ARRESTED		DEAD	
		NO.	%	NO.	%	NO.	%
SATISFACTORY	235	114	48	44	18	52	22
PARTIAL	245	28	11	29	12	142	58
NO FREE SPACE	120	7	5	11	9	80	66

IMPORTANCE OF SATISFACTORY COLLAPSE

It has been shown that the character of the pneumothorax plays a vital rôle in end-results. Table 10 shows the character of the pneumothorax in the clinically well, arrested and dead groups. Thus, of our 600 cases, 149 are clinically well, and of these 76 per cent were satisfactory-collapse cases; whereas only 4 per cent were no-free-space cases and therefore recovered by the usual sanatorium regimen. Of the 600 cases, 274 are dead; 15 per cent of these were satisfactory-collapse cases, 52 per cent were partial-collapse cases and 29 per cent had no free space.

Table 11 shows the end-results according to the character of the pneumothorax. The results are interesting, because of our 600 cases there were 235 satisfactory collapses. Of these, 48 per cent are clinically well and 22 per cent are dead; whereas of 120 cases, having no free pleural space, only 5 per cent are clinically well and 66 per cent are dead.

While a partial pneumothorax is not attended with entirely satisfactory end-results, it is productive of a very beneficial influence, because it holds the disease in abeyance and prevents extension. It is also of value in ameliorating or relieving troublesome symptoms. It might be thought, from a study of the end-results of the partial-collapse cases in table 5, that the procedure is of little permanent value; but a comparative study of the results in the cases in which no free space was found will show that a partial collapse is of unquestionable value, for against 11 per cent clinically well in the partial-collapse group (table 11) there are only 5 per cent clinically well in the no-free-space group. Furthermore, end-results from partial collapses have been unfavorably influenced by reason of the fact that we have been obliged to include 56 partial collapses performed for palliative purposes only, in the desolate bilateral group (clinical group 8), of which 49 died. We have also included 17 partial-collapse cases in the severe, acute infiltrating group (clinical group 4), in which 13 deaths occurred, and 12 partial-collapse cases in the bilateral fibrocaseous cavernous tuberculosis group (clinical group 7) in which 7 deaths occurred. The end-results of partial collapse in these three very unfavorable clinical groups have very materially influenced the end-results as a whole in partial-collapse cases.

INFLUENCE OF PNEUMOTHORAX ON CONTRALATERAL LUNG

In the interpretation of tables 6, 7, 8 and 9, showing results of treatment in cases having an essentially negative noncollapsed lung and those having various types of tuberculosis in the noncollapsed lung, it should be

pointed out, perhaps, that the results of treatment according to the status of the contralateral lung were not necessarily determined by what took place in the noncollapsed lung, because, of infinitely greater importance is what takes place in the pneumothorax side, which is the worse side if the case has been properly selected.

We have already stated that, of 480 collapsed cases, 282 had detectable disease in the noncollapsed lung, but in only 34 instances did it progress demonstrably and become the primary issue, compelling discontinuation of the pneumothorax. Those with bilateral disease who recovered did so in spite of the contralateral lung lesion, because it improved as the worse side improved. Thus, of 194 deaths among our 480 collapsed cases, only 22, or 11 per cent, were attributed directly to progression of disease in the noncollapsed lung. These 22 cases, in which death was attributed to progression of disease in the noncollapsed lung, must not be confused with 62 cases in which pneumothorax treatment was abandoned because of widespread disease, and death followed. These latter cases were all bilateral fibrocaseous cavernous cases and mostly of a desolate character, in clinical group 8, except a few acute infiltrating types belonging to clinical group 4. And, while minor progression of disease undoubtedly took place in the noncollapsed lung of cases abandoned because of widespread disease, progression of disease was not responsible for abandoning the pneumothorax. Furthermore, no unquestionably demonstrable progression of disease took place in the noncollapsed lung of the widespread cases, while under pneumothorax, that could be attributed to the treatment *per se*.

With the above points in mind, table 12 is instructive, because it is obvious that recovery takes place in spite of an active lesion in the noncollapsed lung, if a satisfactory collapse is established in an otherwise suitable case. Thus, there were 174 cases in the fibrocaseous and fibrocaseous cavernous groups (clinical groups 1, 2 and 3) with active fibrocaseous or disseminated bronchogenic caseous infiltrations in the noncollapsed lung. In 65 cases a satisfactory collapse was established, and 42 per cent are clinically well and 25 per cent are dead; whereas in 29 no-free-space cases of the same type none recovered and 76 per cent are dead. There were 49 cases in these same clinical groups with quiescent fibrocaseous infiltrations in the noncollapsed lung. Of these, 21 had a satisfactory collapse, 47 per cent are clinically well and 19 per cent are dead; whereas in 12 no-free-space cases, 2 per cent are clinically well and 33 per cent are dead. There were 97 cases with an essentially nega-

TABLE 12

COMPARISON BETWEEN END RESULTS OF "SATISFACTORY COLLAPSE" CASES AND NO FREE SPACE CASES, AND ALL ACTIVE AND QUIESCENT CONTRALATERAL LUNG LESIONS AND ESSENTIALLY NEGATIVE CONTRALATERAL LUNGS. IN ALL FIBROCASEOUS AND FIBROCASEOUS CAVERNOUS CASES.

STATUS OF CONTRALATERAL LUNG	TOTAL NO. CASES	SATISFACTORY COLLAPSE							NO FREE SPACE						
		NO. CASES	C. WELL	%	ARRESTED	%	DEAD	%	NO. CASES	C. WELL	%	ARRESTED	%	DEAD	%
ACTIVE FIBROCASEOUS AND DISSEM. BRONCHOGENIC CASEOUS INFILTRATION	174	65	29	42	15	23	16	25	29	0	0	3	10	22	76
QUIESCENT FIBRO-CASEOUS INFILTRATION	49	21	10	47	5	24	4	19	12	2	16	2	16	4	33
ESSENTIALLY NEGATIVE	97	56	29	51	11	20	8	14	16	4	25	0	0	9	56

tive contralateral lung in the above clinical groups. In 56 a satisfactory collapse was obtained; 51 per cent are clinically well and 14 per cent are dead. But in 16 no-free-space cases only 4 per cent are clinically well and 56 per cent are dead.

It may be reiterated that, if recovery takes place, it does so more often in spite of whatever disease the contralateral lung had at the beginning of treatment or appeared later, and if death occurs it is more frequently from other causes than extension of disease to the contralateral lung, or its progression if disease is already established there. For instance, among the 174 cases in clinical groups 1, 2 and 3, with active fibrocaseous or disseminated bronchogenic caseous infiltrations in the contralateral lung, there were 79 deaths; but only 12 (15 per cent) were due to progression of disease in the contralateral lung. Again, among the 49 quiescent fibrocaseous infiltrations in the same three clinical groups there were 14 deaths, two (14 per cent) of which were due to progression of disease in the contralateral lung, and among the 97 essentially negative cases there were 23 deaths, only one (approximately 4 per cent) of which was due to extension of disease to the contralateral lung.

Nevertheless, it is evident from the data presented that there is a relationship between the status of the contralateral lung and the results of pneumothorax treatment in any clinical group. Quite naturally, providing all other factors are equal, a patient with essentially negative findings in the noncollapsed lung has a better change for recovery than one with a tuberculous process. The most serious type of disease in the noncollapsed lung is the fibrocaseous cavernous lesion in bilateral cases. In clinical group 7 (bilateral fibrocaseous cavernous tuberculosis) there were 19 collapsed cases, and progression of disease in the noncollapsed lung took place in 3 (15 per cent), two of which were satisfactory-collapse cases and one was a partial-collapse case. The disease was progressively fatal in two cases. Both were satisfactory-collapse cases.

The next most serious type of tuberculosis in the noncollapsed lung is the disseminated bronchogenic caseous infiltration. This was present in 48 cases among the fibrocaseous cavernous and acute infiltrating groups (clinical groups 1, 2, 3 and 4). In 4 (8 per cent) the disease became progressive, and all were fatal. Next in order of seriousness is the active fibrocaseous infiltration, which was present in 144 cases in the above clinical groups (1, 2, 3 and 4); and, while it more frequently became progressive (17 cases, 12 per cent) than the disseminated bronchogenic caseous infiltration, it was less frequently fatal (5 per cent). There was

little difference between the frequency of demonstrable progression in deep peribronchial infiltrations and quiescent fibrocaseous infiltrations, the former occurring in 5 per cent of 105 cases in clinical groups 1, 2, 3 and 4 and the latter in 6 per cent of 53 cases in the same clinical groups; and both were equally serious, being 4 per cent fatal. Undoubtedly, of the various types of contralateral lung disease, the deep peribronchial infiltrations are the most favorably influenced by a pneumothorax on the opposite side.

Progression of disease in the noncollapsed lung most frequently took place in cases presenting acute infiltrating, caseous pneumonic and caseous bronchopneumonic types of disease on the collapsed side (clinical group 4, 17 per cent) and least frequently in the more or less stationary fibrocaseous cavernous types with cavity manifestations in the foreground (clinical group 3, two per cent). In the bilateral fibrocaseous cavernous types (clinical group 7) progression took place in 15 per cent. In the progressive fibrocaseous cavernous types (clinical group 2) progression took place in 8 per cent and in the fibrocaseous group (clinical group 1) progression occurred in 7 per cent.

Progression of disease in the noncollapsed lung took place more frequently in the partial-collapse cases (9 per cent of 245 cases) than in the satisfactory-collapse cases (4 per cent of 235 cases). This would indicate that, instead of progression of disease in the noncollapsed lung being due to the pneumothorax on the opposite side, it more frequently takes place in spite of the pneumothorax and because of its failure to prevent progression of disease in the noncollapsed lung or extension of disease from the partially collapsed side through failure to close cavities. While the number of cases in which progression of disease occurred in the noncollapsed lung is small and justifies no conclusions, it seems reasonable to assume that progression of disease takes place less frequently in the contralateral lung of satisfactory-collapse cases because the mediastinum is more likely to be labile and altered pressure conditions affect both sides. Consequently, the danger of bronchogenic extension is lessened by satisfactory closure of cavities. On the other hand, in partial-collapse cases adhesion formation is more likely to fix the mediastinum; consequently, the pneumothorax changes the intrapleural pressure on the treated side mostly, if not entirely, while the contralateral lung is more or less uninfluenced by pressure conditions, and, as pointed out, bronchogenic extensions to the noncollapsed lung are favored because of failure to close cavities on the more diseased side.

Many clinicians maintain that the presence of a well-defined tuberculous process in the contralateral lung contraindicates pneumothorax treatment, especially if the process is active. This attitude is too dogmatic and extreme. If all patients are denied pneumothorax treatment because of the mere presence of disease in the opposite lung, some of them would be deprived of a valuable procedure which offers, in many instances, the possibility of a complete cure or at least an arrest of their disease.

Our records show that we have obtained excellent results in some cases in which active disease extended from the apex to the third rib in front and the spine of the scapula behind. Yet, in spite of this, a satisfactory collapse of the more diseased lung has been accomplished, and we have noted a steady improvement in the opposite lung leading to recovery. Râles have disappeared; and a comparative study of serial roentgenograms, taken at monthly intervals, has revealed an absorption of areas of increased density, or the shadows have become sharply circumscribed, indicating encapsulation.

If one has to deal with a very active process in the contralateral lung, it is better to allow this activity to subside somewhat before instituting pneumothorax treatment; but this always involves the danger of adhesions forming in the meantime, rendering a subsequent pneumothorax impossible.

We have eliminated this danger in many of our cases by introducing only sufficient gas to separate the lung from the chest wall and maintaining a very slight degree of collapse, in the meantime observing the behavior of the opposite lung. On numerous occasions we have noted the beneficial influence of a minor degree of collapse on the more diseased lung and have been agreeably surprised to observe a retrogression of activity in the contralateral lung.

From a clinical standpoint, in the presence of a satisfactory collapse, any unexplainable fever or unexplainable quantities of bacilli-laden sputum should put one on the alert for changes in the opposite lung.

In dealing with cases which present disease in the contralateral lung, one is frequently confronted with the problem of determining the source of bacilli-laden sputum in patients who are well collapsed, and in excellent general condition and afebrile. A solution of this problem is important for the reason that, if the bacilli-laden sputum is proceeding from the collapsed side, more collapse or compression is indicated, whereas, if the sputum has its source from the noncollapsed side, additional collapse

or compression is contraindicated. In order to arrive at a solution of this problem, one must search for evidence of progression in the contralateral lung. The amount of moisture, character of râles and their exact topographical distribution should be recorded and compared carefully with the results of the previous examinations. The roentgenograms should be studied and compared with all previous ones.

If, after these examinations, it has been found that the disease has not extended beyond or progressed within the original confines, then one is justified in additional collapse or compression, as the case demands. If this is followed by persistent increase in sputum quantity, or if it is followed by a febrile reaction, then the interval between inflations should be lengthened, permitting slight reëxpansion, thus relieving the contralateral lung, and the effect should be carefully noted.

INFLUENCE ON FEVER, WEIGHT AND SPUTUM

In determining the results of treatment of pulmonary tuberculosis, by means of artificial pneumothorax on patients undergoing at the same time the usual sanatorium regimen, it is difficult at times to decide which measure has been of greatest value. Consequently, our no-free-space cases are included for comparison, because, aside from collapse therapy, their treatment was the same as that of the pneumothorax cases, except that they were not under observation as long as the satisfactory-collapse cases, but they were under observation slightly longer than the partial-collapse cases. A summary of our observations regarding the influence of pneumothorax on fever, weight and sputum is shown in table 13. Important points in the summary are as follows:

Fever: Of 235 cases comprising the satisfactory-collapse group, 203, or 86 per cent, were febrile before pneumothorax treatment and 152, or 77 per cent, became afebrile. Among 245 partial-collapse cases, 224, or 91 per cent, were febrile before treatment and 78, or 34 per cent, became afebrile. In the no-free-space group, comprising 120 cases, 110 (91 per cent) were febrile before pneumothorax was attempted and 34, or 30 per cent, became afebrile as a result of sanatorium regimen.

Sputum: Of 235 satisfactory-collapse cases, 176, or 70 per cent, had a positive sputum before pneumothorax treatment and 123, or 70 per cent, became negative after treatment. Of 245 partial-collapse cases, 227, or 90 per cent, had a positive sputum before treatment and 57, or 25 per cent, became negative. Of 120 no-free-space cases, 111, or 92 per

TABLE 13

INFLUENCE OF PNEUMOTHORAX CHARACTER ON FEVER, SPUTUM, AND WEIGHT

CHARACTER OF PNEUMOTHORAX	NO. OF CASES	FEVER													SPUTUM TUBERCLE BACILLI							WEIGHT								
		DURATION BEFORE				DAILY AVERAGE MAXIMUM BEFORE			TIME REQUIRED FOR NORMAL TEMPERATURE				% BECAME AFEBRILE		BEFORE			AFTER			% RENDERED NEG.	LOSS				GAIN			% GAINED WEIGHT
		UNKNOWN	LESS THAN 3 MO.	3 TO 6 MO.	6 MO. OR MORE	99 TO 100	100 TO 101	101 OR MORE	LESS THAN 2 MO.	2 TO 3 MO.	3 TO 6 MO.	6 MO. OR MORE			CONCENTRATION NEG.	CONCENTRATION POS.	POSITIVE SMEAR	CONCENTRATION NEG.	CONCENTRATION POS.	POSITIVE SMEAR		BEFORE		DURING		DURING AND AFTER			
																						LESS THAN 10 LBS.	10 TO 20 LBS.	OVER 20 LBS.	LESS THAN 10 LBS.	OVER 10 LBS.	LESS THAN 10 LBS.	10 TO 20 LBS.	20 LBS. OR MORE	
SATISFACTORY	235	39	84	38	42	107	53	61	55	37	36	24			47	6	170	147	8	45		46	69	39	12	5	41	71	93	
		203			86	203			152				77			176			53		69	154			17		205			87
PARTIAL	245	43	67	52	62	77	49	98	34	18	16	10			10	5	222	54	13	157		37	81	53	32	16	67	75	38	
		224			91	224			78				34			227			170		28	171			48		180			73
NO FREE SPACE	120	20	34	22	34	48	19	43	16	9	7	2			3	4	101	17	12	82		20	50	26	18	4	31	25	27	
		110				110			34				30			111			94		15	96			22		83			69
TOTAL	600	537				537			264						60	514		218	317			421			87		468			

cent, had a positive sputum when pneumothorax treatment was attempted and 17, or 15 per cent, became negative as a result of sanatorium treatment.

Of our series of 600 cases, 514 had a positive sputum and 218 became negative by concentration methods of examination (Ellermann and Erlandsen). Of the 218 which became negative, 147, or 69 per cent, were satisfactory collapses; 54, or approximately 25 per cent, were partial collapses; and 17, or approximately 8 per cent, were no-free-space cases.

Weight: Among the 235 satisfactory-collapse cases, 65 per cent had lost weight before treatment, 7 per cent lost weight during pneumothorax treatment and 87 per cent gained weight during pneumothorax treatment. Of 245 partial-collapse cases, 69 per cent had lost weight before treatment, 11 per cent lost weight during pneumothorax treatment and 73 per cent gained weight during and after pneumothorax treatment. Among the 120 no-free-space cases, 80 per cent had lost weight before sanatorium treatment, 18 per cent lost weight during sanatorium treatment and 69 per cent gained weight during and after sanatorium treatment.

These data, at the first glance, suggest that the results of treatment in the satisfactory-collapse cases were better than in the partial-collapse or no-free-space cases, because the satisfactory-collapse cases were earlier cases, the partial-collapse more advanced, and the no-free-space cases the most advanced. However, such is not the case, although the clinical groups in table 5 (except clinical groups 5 and 6) are arranged somewhat according to their prognosis, the most favorable being clinical group 1 and the most hopeless clinical group 8. The impression that the satisfactory-collapse cases were earlier cases and the no-free-space cases were more advanced finds no support when one notes that satisfactory collapses were proportionately no greater in clinical groups 2 and 3 than partial collapses, and even in the acute infiltrating types (clinical group 4, table 5) there were many more satisfactory-collapse cases than no-free-space cases. Also, in the bilateral fibrocaseous cavernous (none of which could possibly be considered earlier types) the number of satisfactory-collapse cases fairly well approaches the no-free-space cases; yet a comparison of the clinically well and dead furnishes abundant evidence that recovery did not take place because a case was of a more favorable type, but (all other factors being equal) because a satisfactory collapse or even a partial collapse gives a case in any clinical group a better chance for recovery or arrestment of disease than no pneumothorax at all.

In our series of 600 cases, there were 281 cases belonging to the *N. T. A. Stage III C.* Of these, a satisfactory collapse was established in 29 per cent, a partial collapse was obtained in 50 per cent, and in 21 per cent no free pleural space was found.

Of 235 satisfactory-collapse cases in our series, 86 per cent were febrile before treatment. In 18 per cent fever had been present six months or more, and in 30 per cent its daily average was 101°F. or over. Of the 245 partial-collapse cases, 91 per cent were febrile before treatment, while in 25 per cent fever had been present six months or more and in 43 per cent its daily average was 101°F. or more. The 120 no-free-space cases also were 91 per cent febrile before pneumothorax was attempted, and in 28 per cent the fever had existed six months or more; however, 38 per cent had a daily average of 101° or more. Therefore, the percentage of febrile in the partial-collapse and no-free-space cases was the same, but the duration of fever was somewhat longer (3 per cent) in the no-free-space cases, while its daily average maximum was higher in the partial-collapse cases (5 per cent).

Regarding loss of weight, 65 per cent of the satisfactory-collapse cases had lost weight before treatment, while 69 per cent of the partial-collapse cases and 80 per cent of the no-free-space cases had lost weight prior to treatment. However, 12 per cent had lost over 20 pounds in the satisfactory-collapse cases and 21 per cent had lost over 20 pounds in each of the partial-collapse and no-free-space cases. Relatively, then, the loss was greater in the partial-collapse cases.

The sputum findings, as to tubercle-bacilli content, according to the character of the pneumothorax, was as follows:

In the satisfactory-collapse cases, 75 per cent were positive before treatment and 25 per cent had a daily average of 20 cc. or more. In the partial-collapse, 92 per cent were positive before treatment and 40 per cent had a daily average of 20 cc. or more; in the no-free-space cases, 91 per cent were positive before pneumothorax treatment was attempted and 39 per cent had a daily average of 20 cc. or more.

Among our 600 cases, 284 had serious tuberculous complications before treatment, such as laryngitis, enteritis and severe hemoptysis.

The satisfactory-collapse cases had serious tuberculous complications in 43 per cent of all cases, but the partial-collapse cases had serious tuberculous complications in 52 per cent of all cases and the no-free-space cases had serious tuberculous complications in 45 per cent. It seems probable that the value of a partial collapse may lie, not so much in the

actual lung collapse which often is slight and transient, as in the secondary pleuritic thickening with adhesion formation, which takes place following the obliterative changes incident to gas introduction.

Although we have many interesting data on these points, the scope of this paper does not permit their discussion.

SUMMARY

1. Of the 600 cases comprising this study, 480 received actual pneumothorax treatment. Of these, 235 were satisfactory-collapse cases and 48 per cent are clinically well, 18 per cent are arrested and 22 per cent are dead. Of the 245 receiving only a partial collapse, 11 per cent are clinically well, 12 per cent are arrested and 58 per cent are dead.

2. Provided external conditions are favorable and there are no contraindications, the percentage of clinically well, arrested and dead varies greatly, depending, in the order of their importance, upon (1) type of disease, (2) character of the pneumothorax and (3) status of the contralateral lung.

3. The most favorable results were achieved in the chronic fibrocaseous types of tuberculosis without demonstrable excavation, when adhesions did not prevent a satisfactory collapse, and with essential freedom from disease in the noncollapsed lung.

4. In the progressive fibrocaseous cavernous types, with lesions more destructive in character and more widespread, the end-results are correspondingly less satisfactory.

5. Of 423 cases in the fibrocaseous and fibrocaseous cavernous groups, a satisfactory or partial collapse was established in 345. In 182, or 52 per cent, there was demonstrable disease in the contralateral lung, and in 145, or 42 per cent, it was active. Of these, 32 per cent are clinically well, 20 per cent are arrested and 32 per cent are dead. Among 78 no-free-space cases in the same clinical groups, 52 per cent had demonstrable disease in the contralateral lung and in 36 per cent it was active; however, only 8 per cent are clinically well, 10 per cent are arrested and 56 per cent are dead.

6. In actively advancing, caseous pneumonic and caseous bronchopneumonic types (clinical group 4), in spite of statements to the contrary, one sees splendid results, providing a satisfactory collapse can be established and there are no contraindications. But in no class of cases is a satisfactory collapse so vital.

7. In bilateral fibrocaseous cavernous cases, providing the disease on the noncollapsed side is quiescent or at least not actively progressive, one often sees good results following collapse on the more diseased side, also providing a satisfactory collapse is obtained.

8. In desolate bilateral cases, according to our present views, a pneumothorax is justified as a palliative measure in only a few selected cases. The benefits are slight and never lasting, but it does often give relief from troublesome cough and hemoptysis.

9. In unilateral cavity cases, the sooner a pneumothorax is established, the better; not only is danger of intestinal infection diminished, but the possibility of bronchogenic extension on the same side and to the other side is lessened.

10. While it is desirable to have the disease confined to the one side, the presence of even active disease in the contralateral lung does not contraindicate pneumothorax treatment, provided it is not too extensive or of an acute infiltrating or rapidly advancing character.

Of our 600 cases, 472, or 62 per cent, had disease in the noncollapsed lung; and in 359, or approximately 60 per cent, it was demonstrable; and it was active in 206, or more than 34 per cent. Yet demonstrable progression while under treatment took place in only 34 of the 480 collapsed cases.

Of much greater importance than the presence of disease in the contralateral lung is the establishment of a satisfactory collapse on the more diseased side. Of 174 cases in the fibrocaseous and fibrocaseous cavernous groups, with active disease in the contralateral lung, 65 had a satisfactory collapse and 42 per cent are clinically well, 23 per cent are arrested and 25 per cent are dead. While in 29 no-free-space cases, of the same clinical type, none is clinically well, only 3 per cent are arrested and 76 per cent are dead. In the same clinical groups there were 49 cases with quiescent disease in the contralateral lung and a satisfactory collapse on the worse side; 47 per cent are clinically well, 24 per cent are arrested and 19 per cent are dead; while of 12 no-free-space cases of the same clinical type 16 per cent are clinically well, 16 per cent are arrested and 33 per cent are dead.

Progression of disease more frequently took place in partial-collapse cases (9 per cent) than in the satisfactory-collapse cases (4 per cent). Improvement in the contralateral lung is often coincident with and dependent upon improvement of the collapsed lung. Therefore, with disease on the opposite side, the odds are in favor of the patient that the

disease will not progress, and especially if the collapse is satisfactory; and even in partial-collapse cases the odds are still in favor of the patient that the lesion will not progress.

The most serious type of contralateral lung disease is the fibrocaseous cavernous lesion. Disseminated bronchogenic caseous extensions in the contralateral lung are serious and, while less often provoked to progression than a fibrocaseous lesion, they are far more fatal.

Deep peribronchial and quiescent fibrocaseous lesions in the contralateral lung are relatively benign if a satisfactory collapse is established on the more diseased side.

11. Tuberculous laryngitis usually improves with improvement of the lung process and is not a contraindication *per se*.

12. Tuberculous enteritis, if interfering with the patient's nutrition and not responsive to treatment, is probably a contraindication for pneumothorax.

13. The "gas embolism-pleural shock" symptom complex occurred 19 times in over 12,000 inflations or attempted inflations, and in two cases was fatal.

14. Tuberculous empyema occurred in 12 per cent of 480 collapsed cases, but it was not a serious complication unless open drainage procedures were established.

15. Serous exudates were demonstrable in practically every case at some time during the course of pneumothorax treatment, but as long as it remained serous it was never a serious complication.

16. Spontaneous pneumothorax occurred in 16, or 3 per cent, of 480 collapsed cases and three were fatal.

17. Pleurisy with effusion on the noncollapsed side occurred seven times.

18. Progression of disease in the noncollapsed lung took place in 34 cases.

19. Adhesions are almost invariably present in cases demanding a pneumothorax and constitute the greatest obstacle to establishing a satisfactory collapse.

20. The results of treatment in the satisfactory-collapse cases and no-free-space cases indicate the justification of utilizing pneumothorax treatment earlier in the course of tuberculosis than has been generally customary. We feel that it is often a mistake to delay pneumothorax treatment and subject a patient to a prolonged trial of sanatorium treatment.

ARTIFICIAL PNEUMOTHORAX WITH NECROPSY

Report of Seven Cases

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The following seven necropsies show some of the reasons for the failure to accomplish good results after artificial pneumothorax. The first case manifested immediate clinical improvement with rapid relapse and death due to spontaneous pneumothorax on the good side; the second, spontaneous pneumothorax on the left side with immediate death from shock, twenty-four hours after artificial pneumothorax on the right; the third, protracted clinical improvement, yet from the necropsy findings no practical improvement in the pathological condition, and death resulted from infection of the pneumothorax; the fourth, no improvement, and death resulted from spontaneous rupture of the lung into the artificial pneumothorax, producing a pyopneumothorax; the fifth, no improvement, and possibly aggravation of the massive caseous condition by the one pneumothorax injection; the sixth, no improvement, and death resulted from the natural advance of the caseous condition; and the seventh, no improvement, due to extensive disease on the other side.

No. 1: Male, aged 22. Admitted to White Haven Sanatorium, February 26, 1922; died, August 15, 1922. Occupation, mine surveyor in association with a mining engineer. Father and mother, three brothers and four sisters living and well; one brother and one sister died at birth. Grandparents, also, appeared to be free from tuberculosis; no exposure to contagion discovered.

First symptom of illness, one small hemoptysis on September 28, 1921; none subsequently. From this time, cough gradually increased till three or four ounces of yellowish expectoration were raised daily. Height, 71¾ ins. Highest weight 168; weight on admission 151; weight July 20, 1922, 146 (New York Life Insurance Company standard, 163). Three examinations of sputum positive; urine, normal. Heart, normal.

Physical examination showed typical unilateral case with infiltration of right upper lobe. The patient gained three pounds during the first three weeks (February 26 to March 20), and gradually lost thereafter. On May 9, after

continued failure to improve, right-sided artificial pneumothorax was decided upon, and injections were begun on May 11, and continued as follows:

May 11, 200 cc.; May 15, 400 cc.; May 22, 300 cc.; May 26, 400 cc.; May 31, 500 cc.; June 6, 600 cc.; June 12, 600 cc.; June 19, 600 cc.; June 24, 600 cc.; June 29, 600 cc.; July 5, 500 cc.; July 10, 500 cc.; and July 14, 500 cc.

On May 11, at the beginning of the injection, the pressure was 7½ negative; at the end 9½ positive. Immediately after the injection on May 15, the patient was dyspneic and manifested a profuse sweat and tachycardia with some cyanosis of the lips and nails. Two days later the dyspnea and cyanosis had disappeared.

After pneumothorax treatment was begun, the cough, expectoration and night sweats improved slightly, and the patient felt stronger. For two weeks previous to the first injection the temperature was 102°; after the third it dropped to almost normal, and remained practically normal for nine weeks. The temperature rose to 101° for one week preceding death on August 15.

Clinical diagnosis shortly before death was tuberculosis of lungs, right artificial pneumothorax with subsequent spontaneous hydrothorax and spontaneous left pneumothorax.

Necropsy: Pathological diagnosis: Right, artificial pneumothorax with subsequent hydrothorax, marked compression of lung, caseous tuberculosis of upper lobe. Left, spontaneous pneumothorax developing from the right artificial pneumothorax; moderate compression of lung. In other words the entire tuberculosis was confined to the right upper lobe.

On account of the diagnosis of bilateral pneumothorax, the manometer needle was introduced into each pleural cavity before the chest was opened, and showed a positive pressure of 8 on the left and of 2 on the right. In addition, a gush of air followed the opening of both pleural cavities.

Internal appearance, liver pushed downwards, so that lower border was below umbilicus. Height of diaphragm, right side, sixth rib; left side, seventh rib. The heart was displaced to the left and downward.

The right parietal pleura was distended over the left lung to the anterior axillary line at a point just above the horizontal mammillary line, gradually receding above and below; in other words, the artificial pneumothorax had extended the right pleural cavity well across the left lung. The pleural cavity also showed a hydrothorax of 900 cc. of clear straw-colored fluid. The left showed a pneumothorax over the lower part of the lung anterolaterally.

The left lung was compressed to about half normal size. The visceral pleura was thickened over the apex; also toward the mediastinum by the extension of the right pneumothorax over it. On section the lung showed considerable anthracosis, but no tuberculosis. In spite of the anthracosis and compression, there was no increase in fibrous tissue. The bronchial lymph nodes were not enlarged.

The right lung was completely collapsed, though it still remained attached to the costal margin by dense fibrous bands, two running from the costal apex to the lung, one from the lateral chest wall, one posteriorly, and one from the diaphragm. The anterolateral aspect of the lower lobe was covered with thickened pleura about 2 mm. in thickness, due to the presence of the hydrothorax. The lung was compressed to about one-fourth normal size. On section it showed marked compression of the parenchymatous tissue with marked anthracosis, but no increase of fibrous tissue. The tuberculosis was practically limited to the upper half of the upper lobe. The extreme apex showed one-half dozen caseous tubercles about the size of a pea, filled with caseous material, manifesting no tendency to heal. At the apex internally was a small cavity, about 1 cm. in diameter, containing soft caseous material; the wall of this cavity was of extreme thinness. The outer part of the apex showed three masses of caseation about the size of a marble. There were three or four other caseous tubercles about the size of a pea, scattered throughout the rest of the lung. The bronchial lymph nodes were not enlarged.

Apart from the compression produced by the pneumothoraces, all of the left lung and three-fourths of the right lung appeared to be air-containing.

None of the organs in the abdomen, not even the mesenteric glands, showed tuberculosis. The skull was not opened.

REMARKS

(1) *Cause of death:* Right artificial pneumothorax which, extending across the mediastinum at the second rib into the left chest, ruptured into the left pleural cavity and produced a left pneumothorax.

(2) The necropsy showed the exactly typical form of tuberculosis in which artificial pneumothorax would seem to be indicated, namely, a small amount of caseous tuberculosis occurring unilaterally, with no spontaneous tendency to heal. In spite of this, however, the artificial pneumothorax aided little if at all. The amount of tuberculosis found at necropsy was apparently the same as when the patient was admitted to the sanatorium, so that there is a possibility that the pneumothorax aided toward preventing its advance. It gave no help, however, toward actual cure. The compression of the lung produced no increase in fibrous tissue.

(3) I have at present two clinical cases gradually approaching death after more than fifty injections. These cases show a caseous condition with no natural tendency toward cure, and the compression did not change this tendency. In both cases the pneumothorax apparently prolonged life, and allowed the patients out of bed for a short while, but they never reached exercise and are gradually retrogressing.

No. 2: Male, aged 31. First seen January 24, 1908; died October 10, 1919. Occupation, at first medical student and later physician. During the eleven years he was followed as a patient he never manifested the slightest capability of cure. When first seen he showed active infiltration of about two-thirds of the right upper lobe. On rigid regimen for six months, the activity quieted, but on overwork at school it lighted up again, and, as time progressed, it required less and less work to inaugurate activity. About 1916 the disease became active in both lungs, and from this time till death it never quieted again. The extent on the right being much greater than on the left, he himself suggested artificial pneumothorax on the right. He stood the operation poorly, and only a small amount of gas was introduced. The next day he was seized with sudden dyspnea, and died in a few minutes. Necropsy revealed small artificial pneumothorax on the right and large spontaneous pneumothorax on the left. I did not see this particular necropsy, but since only one injection was given and the patient died within such a short time, the only interesting feature to be reported is the development of the spontaneous pneumothorax following artificial pneumothorax on the other side.

No. 3: Male, aged 29. Nativity, Greece. Admitted to White Haven Sanatorium, May 31, 1921; died August 6, 1922. Candy-maker. Father and mother and four brothers and sisters well. History, operated upon for fistula-in-ano in 1915. Last illness began with cough October, 1920; during the ten months before death he had six series of hemoptyses.

Height, 64 inches. Highest weight, 145; weight on admission, 115 (New York Life Insurance Co. standard, 134). Slightly clubbed fingers and curved nails. Sputum, positive on two examinations; urine, normal.

Previous to admission to the White Haven Sanatorium, he had been a patient in the Jefferson Hospital Department for Diseases of the Chest, from March 10, 1921, to May 31, where his temperature had been 101°–102° almost daily till pneumothorax treatments were begun on May 7, when it dropped below 100°, and remained low thereafter. He had, in the Jefferson Hospital, three injections, on May 7, May 11 and May 20. The pneumothorax treatments, therefore, were continued at the White Haven Sanatorium. Physical examination on admission to Jefferson showed, left, cavity taking up most of upper lobe with scattered tubercles below; right, small cavity at apex and scattered tubercles below. The left was distinctly the worse.

Physical examination, on admission to White Haven, showed the heart definitely pushed to the right, the apex being almost behind the sternum, and the right border 3 cm. to the right of the sternum. The left chest showed all the signs of artificial pneumothorax over the entire chest; the right showed infiltration of the upper and the apex of the lower lobe, with apparently scattered tubercles over the remainder of the chest anteriorly, and to the angle of the scapula posteriorly.

For fifteen weeks he held his admission weight of 115 pounds. He then began to lose and lost at the rate of one to three pounds a week, until November 10, when he weighed 105 pounds. During this time, as well as previously, the pneumothorax injections were given at intervals of ten days to two weeks. There was no change in the pneumothorax record, the pressure remaining about 2 positive. From November 10 till March 23 he gained eight pounds by small weekly gains, the pneumothorax injections being continued every two weeks, and the pressure remaining positive at from 3 to 8, or occasionally more. During this period there were one or two short acute flare-ups in temperature, but of no duration.

On March 23, he started to lose weight rapidly and became bedridden. On April 4, the temperature rose and never became normal thereafter, the range being between 100° and 102°. Only three pneumothoraces were given after February 28; namely, on March 15, April 4 and May 10. The one on April 4 was given with difficulty because patient coughed severely.

He had six series of serious hemoptyses, beginning September 21, 1921, lasting seven days and associated with a temperature up to 102.6°; October 14, lasting five days and associated with a temperature of 101.8°; April, 1922, lasting twelve days and associated with a temperature of 102.2°; May 12, lasting twelve days and associated with a temperature of 101.4°; June, lasting two days and associated with no additional rise of temperature above what he was then running, namely, 101°–102°.

The hemoptysis of September 21, 1921, followed a pneumothorax within twenty-four hours; the hemoptysis of October 14 followed a pneumothorax within seventy-two hours; the hemoptysis of May 12 followed a pneumothorax within forty-eight hours.

Necropsy: Pathological diagnosis: Tuberculosis of lungs, left pyopneumothorax. Left pleura, thickened and covered with purulent exudate, adhesions at the apex. Left lung, shrivelled fibrous mass, one-eighth size of normal, containing several flattened-out caseous masses looking as if they had been compressed from previously round caseous masses, varying in size from pea to marble. It was evident that cure of these caseous masses was still remote, though they had been compressed by a successful artificial pneumothorax for more than a year and a half.

Right pleura, adhesions anteriorly and posteriorly and to diaphragm; no exudate. Right lung, very much enlarged. At apex, cavity with smooth walls measuring about 3 cm. in diameter; the rest of the upper lobe showed a few scattered caseous tubercles, varying in size from split-pea to marble, one or two of them being partially hollowed out. The middle lobe was remarkably honey-combed by large cavities. The lower lobe showed small masses of caseation and numerous tubercles with between them areas of congestion. None of the middle, about one-half the lower and about one-half the upper lobes were air-containing.

REMARKS

(1) *Cause of death:* Purulent infection of left artificial pneumothorax and caseous tuberculosis of the right lung.

(2) Three of the pneumothorax injections were followed by hemoptyses within seventy-two hours.

(3) The compressed left lung was entirely fibrous except for the described caseous masses. On account of the fact that pyopneumothorax always produces fibrosis of the underlying lung, the fibrosis was probably the result of this, and not merely of the compression.

No. 4: Female, aged 23. Admitted to White Haven Sanatorium, November 17, 1921; died, May 9, 1922. Examination on admission showed infiltration of right upper lobe. For six weeks she did well, when she developed a right lower lobar pneumonia with temperature of 103.4°. This pneumonia became tuberculous, and, the patient doing badly, artificial pneumothorax was decided upon, and injections given as follows: April 1, 1922, 350 cc.; April 5, 400 cc.; April 11, 300 cc. On account of the fact that she bore the injections badly, and, shortly after the last, became very ill, they were stopped.

Necropsy: Right pyopneumothorax from rupture of lung into previous artificial pneumothorax. The rupture was at the eighth rib and posterior axillary line. The pleura was thickened and covered with greenish pus. The cavity contained about five ounces of thin purulent fluid. Right lung, upper lobe, several large cavities; middle and lower lobes, large conglomerate caseous tubercles in close apposition.

Left pleura, numerous adhesions. Lung, upper lobe, small cavity, 2 cm. in diameter, filled with inspissated pus, exactly in the middle of the lobe with normal tissue all around it. Immediately below, a similar cavity filled with inspissated pus, 1 cm. in diameter. About these cavities there were a few scattered tubercles. All of the tuberculosis on the left appeared to be very acute, and probably occurred within the last nine weeks preceding death. None of the right lung, and 95 per cent of the left lung were air-bearing.

No. 5: Male, aged 26. Entered White Haven Sanatorium March 26, 1922; died, June 16, 1922. In navy from 1917 till 1921. Father and mother living and well; only child. Married five years, wife in run-down condition, and recently quite ill. No children. Height, 65¾ inches. Highest weight, 155 in 1920; 136 in November, 1921 (New York Life Insurance Company standard, 141). Inflammatory rheumatism, both ankles and knees, 1913; influenza, 1918; pleurisy, March 12, 1922. According to patient, illness began middle of January, 1922, with cough. March 12, 1922, spit up several mouthfuls of blood and had chills and night sweats at the same time.

On admission the physical signs showed: right, infiltration of upper lobe; left, infiltration of both upper and lower lobes with a cavity near the angle of the scapula.

Temperature on admission was 100°–101° for six weeks; for ten days it dropped to 99.2° and then went up to 103.2° following a hemoptysis of seventeen ounces on May 18. He had streaked sputum for the next two days and the temperature gradually came down in nine days to 99°. It remained at 99 for two weeks, when he was given a pneumothorax injection of 200 cc. on June 11, and the temperature rose again to 101.8° and was followed by a twelve-ounce hemoptysis the next day. The day following the hemoptysis the temperature was 101.2°; the next day 100.4°; the next day 99.8°, when he had a hemoptysis of 32 ounces and died immediately.

The respirations always remained around 24; the pulse-rate around 100. His weight during the first eight weeks, while he was being weighed, remained practically stationary.

Necropsy: Very well nourished. Practically normal amount of adipose tissue. Left pleura, dense adhesions about upper lobe and between lung and diaphragm. Lung, widespread caseous bronchopneumonic masses from apex to base, varying in size from 2 mm. to 2 cm., the great majority of the latter size. There was a ragged small cavity in the upper lobe, about the parasternal line and second rib. There were a half-dozen cavities, varying in size from 1 to 3 cm., in the lower lobe, the largest one at the situation where a cavity was found clinically. This cavity was on the surface of the lung and the visceral pleura covering it was very thin and congested. It contained a clot of blood, about 2 cm. in diameter, and the bronchi leading from it up to the main bronchus showed coagulated blood. It would appear as if the hemoptysis came from this cavity. Careful search revealed no ruptured blood vessel or aneurysm. A much smaller cavity in close proximity also showed a clot of blood, but no aneurysm or ruptured vessel. The extreme lower portion of the lower lobe posteriorly was air-containing. About 30 per cent of the entire lung appeared to be air-containing. The striking feature about the lung was that, though there was a large amount of involvement, there was no fibrous tissue anywhere. The walls of the cavities were inestimable in their thinness.

Right pleura, few fine adhesions about upper lobe. Lung, caseous tubercle, about 1 cm. in size, at apex of lung posteriorly; remainder of lung normal. Bronchial lymph nodes of both lungs were enlarged and anthracotic.

REMARKS

(1) *Cause of death:* Hemoptysis of thirty-two ounces associated with widespread caseation of left lung.

(2) The process was extremely acute and showed no tendency to heal; it was possibly somewhat quieted by the rest in bed.

(3) The therapeutic pneumothorax of April 12, instead of helping the widespread caseation, possibly stimulated it. The caseation was of such a character and was so widespread as to leave the lung almost a solid mass, with no possibility of compression. It is probable, therefore, that the pneumothorax helped to hasten death, though the patient would surely have died even without it. The pneumothorax was evidently justifiably performed, since he was definitely not improving on the regular regimen. If it were possible to absolutely diagnose widespread caseation, such as he manifested, the pneumothorax would not be justifiable, but so far physical signs are unable to differentiate between fibrocaseation and pure caseation.

(4) The protean character of tuberculosis, and the difficulty in determining the exact pathogenesis, are well illustrated by the fact that case 1 showed caseation and no tendency toward fibrous tissue formation with practically normal bronchial lymph nodes, and case 5 similar caseation and similar lack of tendency toward fibrous tissue formation, with caseous bronchial nodes.

No. 6: Male, aged 19. Admitted to White Haven Sanatorium, June 2, 1915; died, October 4, 1915. Occupation, laborer. Clinical diagnosis on admission, infiltration right upper lobe. In sanatorium 41 days with very little, or almost no improvement, when he had a hemoptysis (July 12, 1915) of 34 ounces; the next day of 12 ounces, the next day of 6 ounces, and the next day streaked sputum; never spat blood thereafter. On account of the fact that he had not improved, and particularly on account of the hemoptyses, a right artificial pneumothorax was done on July 14, and repeated ten times up until September 27. In spite of the injections, and the fact that he had no further hemoptyses, the disease progressed, and he died on October 4.

Necropsy: Right artificial pneumothorax, lung collapsed. Upper lobe, cavity the size of a walnut and many caseous areas varying in size from a pea to a walnut. Similar caseous areas were also scattered through the middle lobe; the lower lobe was practically a mass of caseation. Left lung, numerous recent caseous tubercles.

REMARKS

(1) Following the pneumothorax, the hemoptyses ceased, though I have other cases in which this effect was not achieved, allowing the possibility, therefore, of coincidence. In addition, I have had a patient, with a series of repeated large hemoptyses, prepared for left-sided pneumothorax on account of the massive lesion being on the left, when the

hemoptyses stopped, and the pneumothorax was not done. She died one week later, and the hemoptyses were found to come from several large hemorrhagic infarcts on the right side.

(2) Compression of the lung failed to have any effect on the progression of the disease.

No. 7: Male, aged 29. Admitted to White Haven Sanatorium, July 19, 1918; died, October 9, 1918. Occupation, elevator inspector. At sanatoria, off and on, for two years previous to admission to White Haven, with gradual conscious advance of the disease for even six years previously. In spite of the fact that bilateral tuberculosis was evident, it appeared to be worse on the left; and, with no improvement occurring, a left artificial pneumothorax was done. He had ten injections between July 19 and October 1, during which the disease on the right progressed rapidly and he died October 9.

Necropsy: Left artificial pneumothorax. Lung, upper lobe, large cavity filled with thick caseous material; lower lobe, practically normal except for the compression. Right upper lobe, large cavity; middle lobe, scattered miliary and conglomerate tubercles; lower lobe, scattered miliary tubercles.

REMARKS

(1) The cavity in the left upper lobe, though compressed, was not otherwise influenced by the pneumothorax, and the tuberculosis on the right apparently became more active.

(2) These cases would appear to show that compression of the lung is capable of holding up the advance of the disease, but does not change the patient's predisposition toward it; if the patient has no capability toward the formation of fibrous tissue, compression does not create this capability.

(3) In the past twelve years, artificial pneumothorax has been done on twenty-five of my patients on account of advanced lesions and failure to improve on the regular regimen; four of these twenty-five are living but are practically bedridden; two are untraced and their condition unknown; and nineteen are dead. My experience, therefore, has been that advanced cases, not capable of improvement on the regular regimen, are improved, at most, only temporarily by artificial pneumothorax, and many are not even improved.

SPONTANEOUS PNEUMOTHORAX DURING THE COURSE OF ARTIFICIAL PNEUMOTHORAX

With a Report of Seven Interesting Cases[1]

I. D. BRONFIN

In the light of our present knowledge of the anatomic changes that take place in the relationship between the visceral and parietal pleurae and the lung, as a result of acute or chronic inflammations, and with a better appreciation of the rather complicated mechanism of pneumodynamics, it is surprising that the accident of spontaneous pneumothorax is not of more frequent occurrence. Some authors believe that its frequency is greater than is generally supposed, and that a large number are not diagnosed. This is particularly true of the small or partial pneumothoraces, which usually do not give rise to any striking symptoms or characteristic physical signs, as was well pointed out by Barlow and Thompson (1) in their monograph on the subject.

With induced pneumothorax gaining daily in popularity as a therapeutic measure, one would expect an increase in the incidence of spontaneous pneumothorax, in view of the greater liability of rupture of pleural adhesions from increased intrathoracic pressure. If we accept Duboff's (2) belief that all purulent pleural effusions in tuberculosis are due to lung rupture, then we must attribute the greater number of effusions arising in the course of collapse therapy to spontaneous pneumothorax. The frequency of pleural effusions is known to every pneumothorax operator who observes his cases fluoroscopically. The symptoms prior to the appearance of fluid, such as varying degrees of pain, slight or moderate dyspnoea and a rise in temperature, are at least suggestive of a spontaneous pneumothorax. The amelioration of the symptoms coincident with the appearance of demonstrable fluid points to the possibility of the latter being a factor in sealing up the opening in the visceral pleura, preventing further embarrassment from increased pressure.

[1] From the Sanatorium of the Jewish Consumptives Relief Society, Sanatorium, Colorado.

The accident of spontaneous pneumothorax has been said to be due to a comparatively rapid change in intrathoracic pressure. This is doubtful, as operators have long since established a routine not to give more than 300 cc. of air at the initial operation, even when a large space is obtained. Experience has taught us not to give more than 200 cc. of air at the initial collapse, and not to neutralize the negative pressure before the eighth or tenth refill; yet in six or our cases the accident occurred in from three to twenty-four hours after the initial injection. Beggs's (3) theory that a flexible cushion of air, interposed between the lung and the chest wall, is not nearly as good a support to a weak spot in the lung as the bony chest wall itself, is very plausible. This artificially produced anatomic alteration is unquestionably a potent factor in the causation of the accident, especially in that class of patients to whom pneumothorax is offered as a last salvation after the routine sanatorium treatment has failed to give encouraging results. Indeed, the vast majority of our cases belong to that class. The bad lung is invariably extensively diseased, not infrequently giving physical and roentgen signs of cavitation, and rarely is the so called "good" lung free from active disease.

While Beggs's theory has a very strong appeal, it nevertheless does not explain why spontaneous pneumothorax does not occur, sometimes at least, on the uncollapsed side, since it is now generally accepted and has been proved experimentally by Simon (4) and Stivelman (5) that a moderate amount of air between the visceral and parietal pleurae is present on the untreated side in every case of induced pneumothorax, except of course in those with pleural spaces obliterated by adhesions or in those with a fixed mediastinum. A brief review of the literature has disclosed only one case of double spontaneous pneumothorax, recorded by Marshak (6), but no reports of any case of spontaneous pneumothorax of the uncollapsed lung, although there is no doubt about the possibility of the occurrence of such an accident.

The rupture of emphysematous blebs, located immediately underneath the visceral pleura, as a cause of spontaneous pneumothorax has been mentioned by Hamman (7), although the necropsy reports do not mention such findings in the tuberculous. In several of our recent autopsies we have found that adjacent to areas of pulmonic consolidation there were areas of equal or larger size of emphysema that could be recognized macroscopically. In one case we found large areas of marginal emphy-

sematous blebs, each the size of a walnut, with a marked thinning of the corresponding pleura, so that at first the pathologist considered them cavities. A rupture of such vesicles, especially when the lung is separated from the bony chest wall, is readily conceivable. Case 1 in our series was twice the victim of this accident, first on the right and then on the left side, and each time after an initial injection of a small amount of air. It is our belief that, in most of our patients whose course was not complicated by a pleural effusion, the rupture of such marginal bleb was probably the only etiological factor.

Trauma to the lung by the pneumothorax needle as a possible factor was strongly considered, but we are certain that in at least four of our cases the visceral pleura was not punctured, as a large space was readily found at the first attempt in each of those cases. The needles used were of the Floyd-Robinson type, and the points were moderately dull. The skin was incised in each case by a finely pointed bistoury, so as to make it possible to introduce the needle slowly without any undue force, and thus "feel" the several anatomic structures before entering into the free space. Precautions were taken during the process of novocaine infiltration, the needle being only three quarters of an inch long, gauge 27, and we are reasonably certain that the point did not go beyond the parietal pleura.

Webb (8) and his associates reported, in 1914, three cases of spontaneous pneumothorax, occurring within 24 hours of the first therapeutic collapse, without any fatal results. Krause (9) reported, in 1916, four cases. The duration of the collapse was 14 months, 2 months and 36 hours after a single injection of 350 cc. of nitrogen. All of his cases came to autopsy. In three there was found a greatly thinned pleura overlying the cavity, and in the immediate neighborhood there were well formed adhesions that bound that particular area to the chest wall. In 1917 Marshak and Craighead (10) collected from the literature 25 cases, four of their own and 2 from the private practice of Dr. Beggs, making a total of 31 cases. Heise and Krause (11) described, in 1920, a case of spontaneous hemopneumothorax, occurring 24 hours after the initial collapse with 350 cc. of nitrogen, with a final reading of $-4, -0$. At autopsy was found a thinned pleura over a small cavity and tugged by a stout band-like adhesion. A tear was found at that point, and no adhesions were discovered anywhere else over the entire pleural surface.

Cocke (12) reported only one case, in which spontaneous pneumothorax occurred a little over a month after the initial collapse and three

days after the eighth injection of 600 cc. of air, with a final reading of − 5, + 5. Extreme pressure symptoms did not become manifest until twelve days later, on account of a complicating pyothorax, necessitating rib resection and drainage. Kahn's report (13) of 6 cases differs in no way as regards results from those experienced by the other authors, and substantiates the accepted mortality statistics as being about 25 per cent, although in Drache's cases, as quoted by Lord (14), the mortality was 71 per cent.

The diagnosis of spontaneous pneumothorax is readily made in untreated cases by the acute symptoms of circulatory and respiratory distress and by the sudden change in the physical signs of the chest. In treated cases only the symptoms are of great importance; but they vary in character and in degree to such an extent, especially in pneumothoraces of the valvular or closed types, that resort must be had to the roentgen plate for corroborative evidence. From experience we have come to look upon every patient under collapse therapy, when complaining of a sudden onset of moderate or severe pain in the affected side of the chest, increasing dyspnoea and a rise of one or two degrees in temperature, as a probable case of spontaneous pneumothorax, deserving of careful roentgenological study. The appearance of a pleural effusion a few days after the acute onset, coincident with an amelioration of the symptoms, is to us reasonable proof that such accident did occur, and that the opening was sealed off by the protective inflammatory exudate.

The treatment depends upon the type of pneumothorax. The large closed pneumothorax with marked pressure symptoms requires aspiration of air in sufficient quantities to afford relief. When the symptoms are not so severe it is much safer not to interfere, as in interference there is, at least on theoretical grounds, the danger of a reopening of the pleural tear from a sudden reëxpansion of the lung. The open pneumothorax, or the case which obtains spectacular relief from the aspiration of several hundred cubic centimetres of air after a rapid return of all the acute symptoms, requires the permanent introduction into the pleural cavity of a rubber tube connected with longer tube leading to a bottle of sterile water. To prevent subcutaneous emphysema, the sides of the puncture are sealed off with cotton and collodion. This method is, I believe, the most practical way of controlling the pressure symptoms, and it has proved its special value in cases with valvular pneumothorax. One of our cases, not reported in this series, had, after each paroxysm of cough, severe dyspnoea, necessitating the aspiration of 400 to 600 cc. of air.

Infection and subcutaneous emphysema were greatly feared as a result of repeated needling of the chest. After permanent drainage as described above was established, air bubbles could be seen escaping during each expiration for 3 hours or longer. In one case continuous aspiration was necessary for 9 hours before air ceased escaping during ordinary respiration. When this was accomplished, the rubber tubing was clamped. The clamp was, however, removed during each act of coughing, when large amounts of air could be seen escaping through the glass tube. Caution must be exercised not to immerse the latter down the full length of the bottle, so as not to create a mechanical difficulty of overcoming the pressure of a long vertical column of water. It is best, especially when a slightly negative pressure has been established, to have the distal end of the glass tube not more than 5 cm. below the water level. Comparatively little discomfort was experienced by the patients, and no pleural effusion developed in any of the three cases treated by this method. Drastic stimulation, to combat the shock and circulatory embarrassment, and morphine for the pain must not be overlooked.

The appended case reports are illustrative of many of the points enumerated above, and because of their unusual clinical interest essential details are not curtailed.

Case 1: P. F., female, age 25, married, admitted March 23, 1923. Family history unimportant. Pulmonary symptoms became manifest in February, 1922, following an attack of influenza. A definite diagnosis of tuberculosis was first established in September, 1922, after positive sputum findings. Examination of the chest gave signs of a bilateral pulmonary involvement, with major activity on the right side. Because of persistent fever, ranging daily between 99° and 101°F., excessive cough and progressive weakness, induced pneumothorax as an emergency palliative measure was considered justifiable.

On May 25, at 10 A.M., the initial treatment was given. A space was found at the first attempt, recording a manometric reading of −70, −30; 200 cc. of air were introduced with a final reading of −50, −10. No pain whatever was experienced during the treatment and the patient seemed quite comfortable. At 4 P.M. of the same day she complained of a feeling of tightness in the right chest and slight difficulty in breathing. The temperature was 99.6°, pulse 100 and respirations 30. Examination showed both chests to be apparently equal in size, but the whispered and spoken voice was decidedly decreased on the right side in front above the 4th rib. Breathing was also moderately

diminished. This change was at first thought to be due to the introduction of the 200 cc. of air, although it was remembered that such a small quantity was not likely to produce so marked a change in the physical signs. The heart did not seem to be displaced. The possibility of spontaneous pneumothorax was considered, but there was no indication for immediate interference, and it was thought wise not to disturb the patient for roentgen examination. For the same reason the chest was not examined posteriorly. At 10 P.M. the temperature rose to 101°, pulse 120, respirations 26. With the exception of this peculiar feeling of tightness in the chest and slight difficulty in breathing, there seemed to be no changes. Examination of the front of the chest also disclosed no changes. At 8:30 the following morning the patient suddenly experienced an increase in dyspnoea after slight exertion. At 8:45 she was seen to be suffering from marked dyspnoea, and cyanosis was pronounced. The pulse was rapid and thready, the pupils widely dilated and cold and clammy perspiration covered the entire body. A fatal issue seemed imminent. A needle was immediately introduced at the site of the original puncture (4th interspace and midaxillary line) with a manometric reading of −10, +50. Cardiac stimulants were meanwhile administered. After the aspiration of 400 cc. of air, rapid improvement at once set in. Withdrawal of the needle produced a steady, gradual return of the symptoms, manifested by increasing dyspnoea and cyanosis. At 4 P.M. the introduction of the needle recorded the same manometric readings as in the morning. The escape of air at this time, however, was very slow. Withdrawal of the needle disclosed a drop of serous fluid. This was examined and found negative for microörganisms. To combat the increasing dyspnoea, permanent drainage was instituted. Small amounts of serous fluid had to be forced back into the chest cavity by means of a sterile syringe in order to permit the free escape of air. This treatment was continued until the following morning at 10 A.M., when a roentgenogram showed no evidence of air in the pleural cavity. The tube was clamped, but not withdrawn from the chest wall, and there was no return of symptoms. The following day the tube was removed with no ill effects. The wound readily closed.

The subsequent clinical course seemed for a time uneventful. The temperature, with the exception of the initial rise on the day of the accident, continued to be within normal variations. Subsequent roentgenograms showed no evidence of fluid. On June 12, examination revealed a decided decrease in moisture on the right side. The left side, however, yielded signs of increased activity. Low grade fever appeared on July 28, and continued fluctuating daily between 99° and 100.5°. Increased cough and expectoration became troublesome. On October 25 Dr. Beggs, who had seen the case several times, was again called in consultation, and he agreed with the resident staff that there was apparent improvement on the right side and increased activity on

the left. He thought that in view of the grave prognosis it might be worth while to try to collapse the left lung.

On October 27, at 10 A.M., induced pneumothorax was started on the left side. The needle was introduced at the 4th interspace in the midaxillary line. A pleural space was readily found, yielding a manometric reading of −80, −20. One hundred cubic centimetres of air was introduced with a final reading of −70, −20. No pain was experienced during the procedure. Heroin, 1/12 grain, was ordered to be given every 3 hours to allay the cough, and the site of the puncture was strapped with adhesive tape. Orders were given to the nurse to see that the patient remain in the recumbent position and not be allowed to move from side to side, in order to forestall an accident from the slightest exertion. At 4 P.M. the same day the patient complained of slight pain and a feeling of tightness in the left lower chest. Temperature was 100°; pulse 80, regular and of good quality; respirations 22. Examination showed both chests to be of equal size. The heart was not displaced, but the breath sounds were diminished and slightly amphoric in character above the 4th rib. At 8 P.M. there were moderate dyspnoea and cyanosis. Caffeine and strychnine were administered hypodermically. At 10 P.M. 1/6 gr. of morphine and 1/150 gr. of atropine were administered for the relief of the pain and dyspnoea. This was repeated at 4 A.M. and 8:30 A.M. On October 28 there seemed to be no change in general condition, pulse 100, respirations 28, temperature normal. The breath sounds were quite distant and decidedly more amphoric in character. A diagnosis of spontaneous pneumothorax was made and this was confirmed by the roentgenogram.

During the following five days the patient suffered, off and on, from pressure symptoms and moderate pain. These were readily relieved by small doses of morphine and atropine. A plate taken in the vertical position showed a well-established pneumothorax on the left side with a small amount of fluid at the base. The pressure symptoms disappeared within ten days from the date of the accident and the temperature, pulse and respiration continued within normal limits. Chest examination, November 26, showed a decided decrease in moisture on the right side. Refills are now made every two weeks, giving 300 cc. of air each time, with final negative readings. Her general condition is quite satisfactory at present.

Case 2: H. M., male, age 26, occupation tailor, admitted April 7, 1923. Family and previous history unimportant. Onset of pulmonary symptoms in January, 1921, and a diagnosis of tuberculosis was established 3 months later. Received medical attention at several eastern institutions where he had a series of hemoptyses, followed each time by a rapid recovery. Chest examination disclosed evidences of active pulmonary tuberculosis involving the upper half of the right lung, and signs of an inactive fibroid lesion of the left upper lobe.

The roentgen plate confirmed the physical findings. The clinical course was uneventful until May 10, when the temperature suddenly rose to 101° and persisted during the following three days. On June 2 the patient had a hemorrhage, losing about 8 ounces of blood.

In view of the previous history of repeated hemoptyses, and taking into consideration that the left lung seemed apparently free from active disease, induced pneumothorax was started on July 15 at 9:30 A.M. Evidently a large pleural space was found, as could be judged from the high negative readings of −100, −80, with a final reading of −75, −40, after the introduction of 200 cc. of air. Examination of the chest, one hour later, disclosed no changes. This examination was made to determine how much of an alteration in physical signs can result from the introduction of a comparatively small amount of air in an apparently free pleural space. At 8:30 P.M. there was a complaint of slight pain in the right chest. There was no change in the rate of the pulse or respiration, nor was there any rise in temperature. Examination disclosed a moderate subcutaneous emphysema. Percussion gave a tympanitic note in front and in the axilla above the 4th rib. Moderate hyperresonance was present between the 4th and 6th ribs in front, and the area of liver dulness could not be mapped out. Breathing was markedly diminished in the upper half of the chest and nearly absent in the lower half. Râles were not audible at all. There was no evidence of cardiac displacement. A diagnosis of spontaneous pneumothorax was made. This was confirmed by a posterior X-ray plate. At 6:30 P.M. the pulse was 110, respirations 30, temperature 100°F. Slight cyanosis of the lips and fingertips was noticed. At this time the complaints were a feeling of tightness in the chest and difficulty in breathing. A needle was introduced and it recorded a reading of +10, +50. The clinical impression of the case was, however, in favor of pursuing the policy of watchful waiting. Small doses of morphine and atropine were administered hypodermically which seemed to give considerable relief. The following morning the subcutaneous emphysema had spread to the right arm. The dyspnoea was less marked, there was only slight cyanosis, the pulse was of good quality with a rate of 84 and respirations were 24. Cough sedatives had to be administered to allay undue exertion. The general condition seemed to be slightly improved. On July 20 an anterior X-ray plate showed a large pneumothorax, with a line extending from the base up to the 2nd interspace and occupying approximately the outer third of the pulmonic field. On July 30 the patient was semi-ambulant and afebrile. On this date a pneumothorax needle was introduced, and a reading of −60, −25 was obtained, with a final reading of −15, + 15 after the introduction of 150 cc. of air. Since then the patient has been receiving refills every 2 to 3 weeks in amounts of 200 to 300 cc., each time stopping at a final negative reading between −60, −5 or −60 and zero. The general condition has markedly improved.

Case 3: M. S., female, age 39, married, readmitted March 24, 1923. Pulmonary tuberculosis since 1917. She had four periods of residence in the sanatorium, remaining each time 6 to 8 months. Each readmission was due to a reactivation of the disease. Physical and roentgen examinations showed a bilateral pulmonary lesion with probable cavitation at both upper lobes. The clinical impression was that the major activity was on the left side. The pulse, even during an afebrile period, ranged between 95 and 120. On account of active laryngeal and abdominal symptoms she received heliotherapy with encouraging results.

Upon admission she presented the classical signs and symptoms of a left-sided lung rupture. Cardiac displacement toward the right side was marked, and a rather extensive subcutaneous emphysema was also present. The latter was the result of several air aspirations performed at her home by Dr. M. Katzman. On account of a rapid return of circulatory and cardiac embarrassment shortly after another aspiration of 1000 cc. of air, permanent drainage was established and continued for five days. It is worth noting that her temperature was at no time above the normal, although small amounts of serous fluid could be seen escaping at frequent intervals. The fluid was, however, sterile on repeated microscopic examinations.

After five days it became obvious that intrathoracic pressure alone was not responsible for the recurring attacks of dyspnoea, simulating in every respect bronchial asthma. This was proved by the roentgen plate and by the negative manometric readings. Digitalis therapy was therefore started, in the belief that we were dealing here with a condition of cardiac asthma. The splendid results obtained from this form of treatment confirmed the diagnosis. The tube was, however, kept in the pleural space until March 26. This was done for two reasons. At times, during an attack of dyspnoea, a large amount of air could be seen escaping through the tube upon removal of the clamp. From this we concluded that the opening in the visceral pleura was not closed. An additional reason was the possibility of pleural effusion. It was thought, in the event of an effusion, to use this tube for the purpose of aspirating the fluid after the Mozingo method. Our fears, however, were unfounded, as regards pleural infection, although an X-ray plate, taken March 31, showed a small amount of fluid at the left base. On April 15 the patient was semiambulant, and by the middle of May all the acute symptoms had disappeared. The X-ray plate, taken on May 2, showed practically a disappearance of the fluid and a considerable reëxpansion of the lung. Examination at this time disclosed evidences of very little activity on the left side with an increasing amount of moisture on the right. While the patient was fairly free from active symptoms, her general course, however, seemed unsatisfactory. Excessive cough and expectoration, weakness, occasional night sweats and pain in the right side of the chest were troublesome symptoms. Physical examina-

tion disclosed a reactivation of the right lung. Induced pneumothorax was therefore started on that side on June 27, with gratifying results. Refills are given regularly every two weeks, stopping at negative readings. The patient is ambulant and afebrile, cough is considerably decreased and there is slight relief from the intestinal symptoms.

Case 4: D. R., male, age 31, occupation clerk. Readmitted February 8, 1923. Pulmonary tuberculosis since February, 1914. Four months later he had a profuse hemoptysis. Recovery was rapid. He was able to pursue his occupation until 1918, the work being interrupted occasionally for a week or two on account of hemoptysis. About this time he began to complain of pain in the lumbar region. X-ray showed early caries of the 4th lumbar vertebra. Immobilization and heliotherapy yielded satisfactory results. In April, 1923, he was once more incapacitated on account of a profuse hemoptysis, necessitating his readmission to the sanatorium. Physical examination gave signs of a bilateral ulcerative lesion, involving the entire right lung, with apical cavitation, and the left upper lobe. He was pursuing a very active febrile course. Induced pneumothorax, as a last resort, was started on the right side on May 14 at 9:30 A.M. A pleural space was readily found, recording a manometric reading of −70, −20, with a final reading of −50, −20, after the introduction of 200 cc. of air. At 2:30 P.M., the same day, the patient complained of slight pain in the right side with increasing dyspnoea. His face wore an anxious expression and cyanosis was pronounced. At 4:30 P.M. a needle in the chest recorded a manometric reading of +20, +60. On account of the patient's moribund condition plates were not taken. Eight hundred cubic centimetres of air were aspirated, resulting in immediate but only temporary relief. At 7 P.M. the needle was again introduced. The manometric readings were +30, +70. One thousand cubic centimetres of air were removed. Because of a return of all the acute symptoms one hour after the last aspiration, continuous drainage was instituted and kept up until midnight of the 16th. At this time it was observed that, with the rubber tube clamped for several hours, only a few bubbles of air would escape after the removal of the clamp. At 2 A.M. on the 17th no air escaped, and it was definitely ascertained that the rubber catheter was not clogged. The general condition, however, became rapidly worse. Cyanosis was marked at 3 P.M., and the respiration assumed a Cheyne-Stokes character at 4 P.M. There was no response to intravenous cardiac stimulation. Death ensued at 5:45 P.M. Postmortem X-ray plates showed a diffuse basal pneumothorax, with a moderately enlarged heart shadow displaced to the left.

Case 5: L. G., female, married, age 40, admitted June 11, 1923. Onset of pulmonary tuberculosis in 1902 with a large hemoptysis, followed by a protracted convalescence, lasting six months. The subsequent course was char-

acterized by several small hemoptyses each year, necessitating her confinement to bed for one or two weeks. In the intervals she was able to pursue her household duties. In 1913 the general and local symptoms increased in severity. Chest examination gave signs of a bilateral ulcerative lesion, with major involvement of the left lung. Induced pneumothorax on the left side was started by Dr. William N. Beggs on November 5, 1913. On March 1, 1914, four days after the fifteenth refill, the patient suddenly experienced a sharp stabbing pain in the left chest immediately after a paroxysm of coughing. Dyspnoea and cyanosis were quite pronounced the next day, and the temperature ranged between 102° and 104°F. Succussion was elicited in a few days. On March 12 several hundred cubic centimetres of straw-colored fluid were aspirated. The second aspiration recovered yellowish-green fluid, which was positive for tubercle bacilli, staphylococci, strepto-bacilli and many pus cells. Repeated aspirations with replacement of air resulted in a steady improvement. About the middle of July she was ambulant and afebrile, and seemed to enjoy a fair degree of health.

The subsequent clinical course was uneventful. Refills were made at irregular intervals, and she was up and about pursuing her usual duties. On June 3, 1923, seventeen days after a refill of 450 cc. of air, she complained of a sharp pain in the left chest, and of "a feeling of tightness as if after a gas injection." The temperature mounted to 101°F. the next day. Upon admission she appeared extremely septic. Horizontal bedside roentgen plates showed a large left-sided pneumothorax, with a marked lateral haziness interpreted at first as thickened pleura. A later plate showed a definite level layer of fluid. A diagnostic puncture was made and 10 cc. of thick creamy pus was aspirated. This was found positive for tubercle bacilli and negative for other microörganisms. The treatment consisted of aspirations, injections of alcoholic solutions of gentian violet or methylene blue, and at times replacement by air. The dye appeared in the sputum three to five minutes after the injection. Slow improvement followed. The patient is now up and about, but the exudate, though small in amount, is still present.

Case 6: M. D., age 37, occupation motorman, admitted November 3, 1922. Pulmonary tuberculosis since 1916. Chest examination gave signs of a bilateral upper lobe lesion. During the following 6 months he had three small hemoptyses, followed each time by fever ranging between 100° and 101°F., lasting for two or three weeks. About the middle of August, 1923, cavity signs on the right side were elicited posteriorly in the region of the 8th dorsal spine. Comparative roentgen plates confirmed the physical findings. The initial treatment was started on September 27 at 10 A.M. A space was not found and the manometer recorded typical intrapulmonic readings. No air was administered. At 8 P.M. the patient complained of severe pain in the

right side of the chest and moderate dyspnoea. There was no change in the physical signs. The following morning fluoroscopy revealed a definitely localized pneumothorax, extending from the base up to the 5th rib. The pain persisted for the next three days. The temperature, pulse and respiration continued within normal variations. Refills are now made every two weeks with satisfactory results.

Case 7: S. S., age 47, occupation merchant, admitted June 14, 1923, with a history of pulmonary tuberculosis of four months' duration. Complaints upon admission were severe, stabbing pains in the right side of the chest, excessive but unproductive cough, fever up to 102°F., moderate dyspnoea and cyanosis. Physical examination gave evidence of a soft lesion, involving the upper two lobes of the right lung, and an inactive fibrosis of the left upper lobe. The roentgen plate showed an extensive ulcerative process of the right lung. Below the 4th rib several bands, interpreted as adhesions, were distinctly visible. Slight rarefaction was noted in the areas of lung tissue included between these bands. The roentgen diagnosis was a probable localized spontaneous pneumothorax.

As the acute symptoms subsided in nine days, active interference was deemed inadvisable, especially when it seemed difficult to obtain the patient's coöperation. A plate, taken on August 13, showed a disappearance of the linear markings, but there was still a small amount of pocketed air between the 3rd and 4th ribs. Another plate, taken on September 26, showed a disappearance of the air and an increase in the tuberculous process, extending down to the base. At this time there was a recurrence of the fever. Physical signs pointed to an increase in activity on the right side.

On November 22, at 11 A.M., an unsuccessful attempt at finding a pleural space was made. Typical intrapulmonic manometric readings were recorded. Soon after the withdrawal of the needle, the patient complained of pain on that side and increasing difficulty in breathing. At 1 P.M. the dyspnoea was quite marked. Examination gave signs of diminished breathing and a disappearance of the râles below the 3rd rib and 6th dorsal spine. The roentgen plate, taken on the following day, confirmed the diagnosis of spontaneous pneumothorax. The acute symptoms gradually subsided without interference. Refills are now made every two weeks. The patient has been ambulant and afebrile during the last ten weeks and has gained twelve pounds in weight.

SUMMARY AND CONCLUSION

A report of our seven cases is justified, as they present many new points of interest. Case 1 began to show pressure symptoms six hours after the initial treatment, and extreme symptoms, necessitating active

interference, twenty-four hours later. Despite repeated punctures of the pleura with needle and trocar, no effusion of consequence developed. The rapid reëxpansion of the lung is another point worth recording. The temperature remained normal. Clinical improvement was noted later in the right lung and increased activity of the left lung. Spontaneous pneumothorax, apparently of the closed type, occurred on the left side six hours after the initial collapse with only 100 cc. of air. Though no operative interference was necessary, some fluid developed with no coincident rise in temperature.

Case 2 is a type of the large closed spontaneous pneumothorax which is frequently overlooked, and the symptoms are often attributed to a reaction following the initial collapse. The extensive subcutaneous emphysema was probably a factor in partially relieving the pressure symptoms.

Case 3, though not properly belonging to this group, is presented to illustrate the importance of considering cardiac insufficiency as a cause for dyspnoea and so called asthma. It is now generally known that the circulatory embarrassment is due to a dislocation of the heart and large vessels, but when the roentgen plates show no marked mediastinal displacement, and very little air escapes through the tube or needle, attention should be paid to the myocardium and proper treatment instituted. In this case the right lung became reactivated, due perhaps to increased function, while the left lung was collapsed. The fact that very little dyspnoea is now experienced with a moderate right-sided collapse proves that the dyspnoeic attacks during the first week following the accident were not entirely due to increased intrathoracic pressure. The rapid improvement under large doses of digitalis is a therapeutic proof that cardiac insufficiency was an important factor.

From case 4 we learn that at times all efforts fail. Death was undoubtedly due to cardiac failure, as the postmortem plates failed to show any pneumothorax of consequence.

Case 5 is unique because of the accident occurring twice, the second time ten years after the first accident. The likelihood of spontaneous pneumothorax was not at all considered, as it was thought that the lung during ten years of compression had become a mere fibrous cord. The successful recovery from the empyema without surgical interference points to the advisability of exercising all known measures, before resorting to open drainage and thereby subjecting the patient to a life of misery.

Cases 6 and 7 prove that when no pleural space is obtained during the first or subsequent attempts the introduction of the needle into the lung is not without danger. Case 7 also illustrates the importance of roentgen examination, as physical signs upon admission gave no indication of an existing pneumothorax.

Attention has thus been called to the frequency of spontaneous pneumothorax. This accident occurred six times in a group of 43 initial cases during a period of ten months. The etiology is obscure in cases with a large pleural space, especially when the accident occurs only a few hours after the initial collapse. The rupture of marginal emphysematous blebs is a strong possibility. Whether these blebs can be recognized on the X-ray plate is a problem worthy of the attention of roentgenologists. It seems that a slight change in the negativity of the intrathoracic pressure is as potent a factor as very high pressures in tearing up adhesions. Sudden onset of pain shortly after a gas refill, coincident with a rise in fever, and the partial or total relief from the acute symptoms after the appearance of an effusion, should be considered at least suspicious evidence of a spontaneous pneumothorax. Sharp pain alone, without fever or a subsequent effusion, does not exclude the possibility of a spontaneous pneumothorax. There is danger of producing a spontaneous pneumothorax from the accidental or intentional introduction of a needle into the lung, even in the apparent absence of a free pleural space. Valvular pneumothoraces require the introduction of a rubber catheter into the pleural cavity for continuous aspiration of air. There is practically no danger of pleural infection from such a procedure. When free drainage of air fails to relieve the circulatory symptoms, digitalis in large doses is indicated. In case an empyema develops, repeated aspirations with or without replacement of air should be persistently tried before resorting to rib resection and open drainage.

The author wishes to acknowledge his gratitude to Drs. W. N. Beggs and A. S. Taussig for their assistance in the management of these cases.

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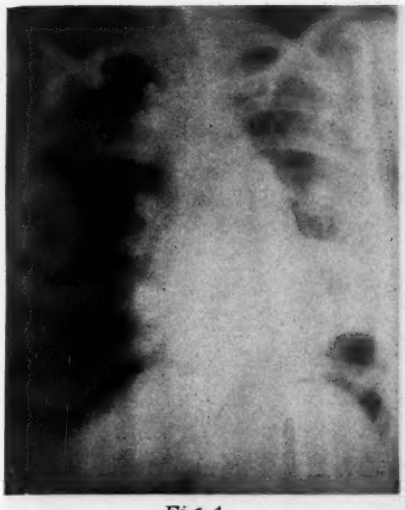

Fig. 1

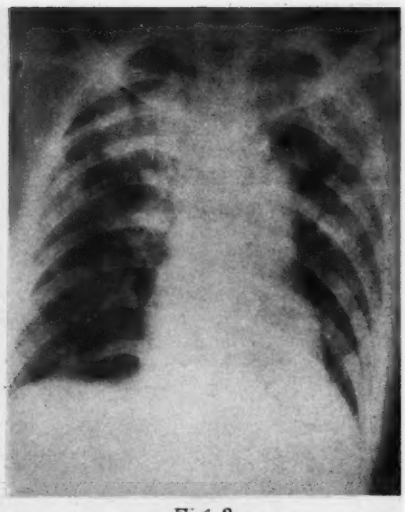

Fig. 2

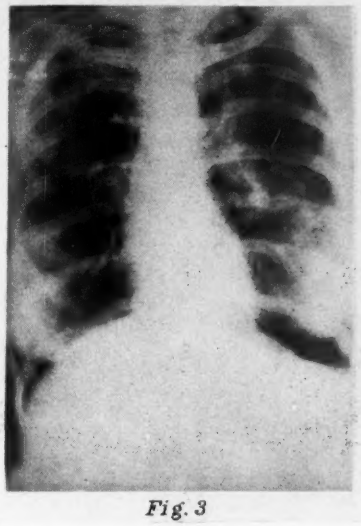

Fig. 3

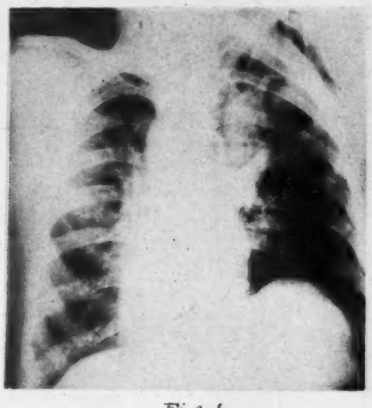

Fig. 4

FIG. 1. CASE 1. ROENTGENOGRAPH TAKEN 24 HOURS AFTER INITIAL COLLAPSE WITH 200 CC. OF AIR
Note extensive pneumothorax

FIG. 2. CASE 1. ROENTGENOGRAPH TAKEN 24 HOURS LATER THAN FIG. 1, SHOWING ALMOST COMPLETE REEXPANSION

FIG. 3. CASE 1. ROENTGENOGRAPH TAKEN 24 HOURS AFTER INITIAL COLLAPSE OF LEFT LUNG WITH ONLY 100 CC. OF AIR
Note extensive pneumothorax

FIG. 4. CASE 2. ROENTGENOGRAPH TAKEN 5 DAYS AFTER INITIAL COLLAPSE WITH 200 CC. OF AIR
Aspiration of air was not necessary

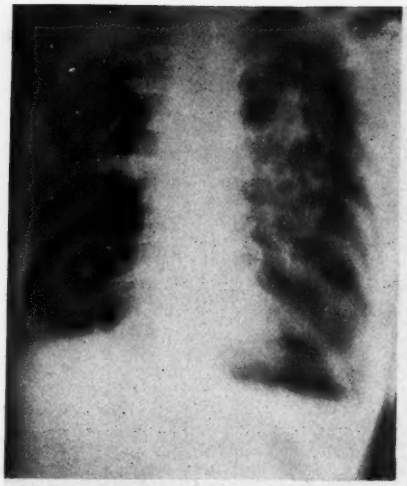

Fig. 5

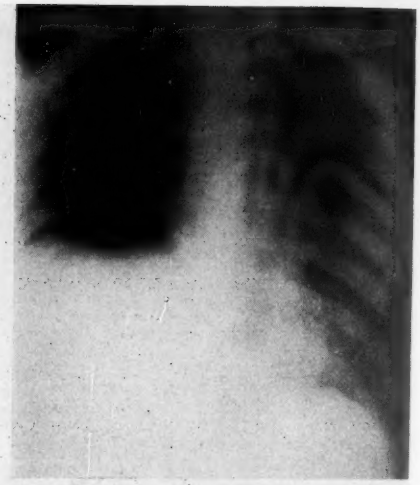

Fig. 6

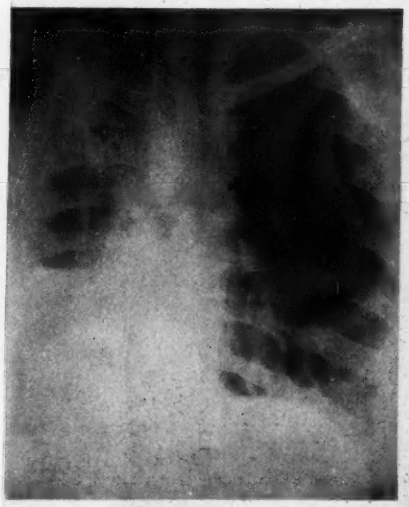

Fig. 7

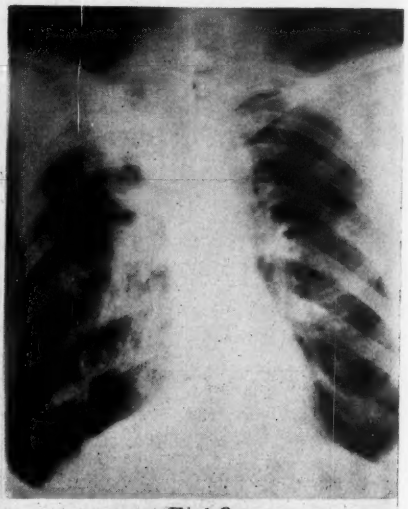

Fig. 8

FIG. 5. CASE 3. ROENTGENOGRAPH SHOWING EXTENSIVE LEFT PNEUMOTHORAX WITH A SMALL EFFUSION

Continuous drainage failed to improve the dyspnoea. Digitalis in large doses proved of great value.

FIG. 6. CASE 5. ROENTGENOGRAPH, TAKEN IN MARCH, 1914, SHOWING LEFT-SIDED PYPNEUMOTHORAX, THE RESULT OF PULMONARY PERFORATION SHORTLY AFTER THE FIFTEENTH REFILL

Successful recovery from aspirations and replacement of air

FIG. 7. CASE 5. ROENTGENOGRAPH, TAKEN IN OCTOBER, 1923, SHOWING A SIMILAR CONDITION AS IN FIG. 6

FIG. 8. CASE 7. ROENTGENOGRAPH TAKEN 24 HOURS AFTER AN UNSUCCESSFUL ATTEMPT TO FIND A PLEURAL SPACE

Note extensive right-sided pneumothorax

Fig. 9

FIG. 9. SHOWING METHOD OF CONTINUOUS ASPIRATION OF AIR IN CASES OF VALVULAR PNEUMOTHORAX

COMPLETE LEFT HEMIPLEGIA, WITH RECOVERY, AFTER ATTEMPTED ARTIFICIAL PNEUMOTHORAX[1]

Report of a Case

SALING SIMON

The foreign literature (1) contains numerous reports of mishaps following thoracentesis for pleural effusions as well as those occurring during the administration of gas to produce therapeutic artificial pneumothorax. On the other hand, the American literature (2) contains comparatively few instances of similar accidents. It is difficult to decide whether this is due to a lower incidence of this condition in America or to the failure of the American physicians to report their cases. Many of the patients reported on in the general literature recovered, although a goodly number of fatalities are recorded. With improved technique the number of these distressing accidents during the administration of artificial pneumothorax has been substantially reduced. More recently, however, as its application has become more universal, there is again noted an apparent increase.

Cordier (3) has classified the symptoms occurring in these accidents into three groups, in the following order of their frequency:

1. Those with symptoms which develop suddenly and resemble syncope and frequently terminate in rapid death.

2. A second group in which convulsions and epileptiform seizures are the initial symptoms.

3. A third group in which hemiplegia and paralysis occur. These may or may not be preceded by a convulsive seizure or by syncope; the motor disturbance usually lasts but a short time and the paralysis may occur either on the same or opposite side of the pleura punctured.

Numerous explanations have been offered for the occurrence of these various symptoms when the thorax is perforated, but the majority of investigators are divided into two main schools upholding different theories as to their cause. There are, first, those who believe with Forlanini that the symptoms can be attributed to a pleural reflex or shock, and second, an equal or even greater number, who maintain

[1] From the National Jewish Hospital for Consumptives, Denver, Colorado.

that the symptoms are due to air emboli which lodge in the cerebral blood vessels. Brauer is a strong advocate of the latter view. He argues that such severe nervous manifestations can hardly be accounted for by reflex disturbances, even though in most instances no emboli can be demonstrated in the brain postmortem, and yet, in those cases in which death has occurred immediately after the puncture of the chest wall, air emboli have in a number of instances been found in the brain at autopsy performed with exacting technique. Air emboli have also been seen in the eye upon ophthalmoscopic examination immediately before and after death, even when a subsequent examination of the brain failed to reveal any emboli to account for the fatal issue.

Stivelman (4), quoting the reports of 867 cases treated by artificial pneumothorax by nineteen American authors, contends that the occurrence of air embolism as a cause for the symptoms resembling syncope has not been proved.

I have attempted to select from the available literature only those cases in which, together with other symptoms, hemiplegia or paralysis developed.

Lemke (5) reports the case of a man, 28 years of age, who had a right-sided artificial pneumothorax and who, at the second filling, performed one month after the initial one, suddenly collapsed, with breathing becoming shallow and pulse small. In a short time consciousness returned, but there remained a right-sided hemiplegia and aphasia which persisted for three months. Wever, commenting on this case, believes that air embolism cannot be excluded as the etiological factor.

Peters (6) states that Sundberg, quoted by Murphy and Kreusher, reported three deaths occurring during the administration of gas for artificial pneumothorax. One, a women of 28, developed syncope as the needle was introduced into the intercostal space and died with hemiplegic symptoms 36 hours later without regaining consciousness. Postmortem examination revealed thrombosis of the small vessels with numerous areas of softening in the cerebral cortex. Death was ascribed by Sundberg to vascular crisis in the cerebrum originating from a pleural reflex.

Lucius Spengler reports the case of a women, Frau D., on whom an artificial pneumothorax was performed and only a moderate compression obtained because of the presence of adhesions. A number of subsequent fillings were given without difficulty. At one of these fillings the patient went into syncope, the pupils dilated and complete recovery occurred in ten minutes. A week later another filling was attempted, when the patient again developed syncope

and became pulseless, and the pupils dilated. Later, tonic convulsions of the entire body occurred and these were followed by a right-sided facial paralysis and tonic convulsions on the right side. The next day the patient became conscious and developed involuntary urination. Death occurred on the third day.

Ivan Peterson (Krabbisholm Sanatorium) reports the case of a farmer, 21 years old, who was receiving artificial pneumothorax treatment on the right side. At the second filling no manometric readings were obtained and the pleural gas pressure was increased to overcome what was believed to be an obstruction in the needle. The patient suddenly became unconscious, there were convulsive twitchings, after one minute vomiting occurred and consciousness was restored but vision was lost. He was unable to raise his right arm, and his right leg felt heavy; five minutes later all symptoms had disappeared. Peterson regarded this as a pleural reflex.

Hansen reports three cases from the Vejlefjord Sanatorium which he regarded due to cerebral air embolism: (*1*) A woman, 40 years of age, in whom only a partial compression of the left lung could be obtained on account of extensive adhesions; at the twentieth filling she became suddenly nervous and restless and paralysis of the right arm developed, followed by recovery in ten minutes. (*2*) A woman, 35 years of age, in whom only a partial compression of the right lung was obtained on account of adhesions, complained of inability to see during the fifth filling, while 20 cc. of gas was being introduced under high pressure. Paralysis of the right arm developed, but there was no loss of consciousness and recovery ensued in five minutes. (*3*) A woman, 32 years of age, became suddenly dizzy and blind during one of her refills, which was followed by paralysis of the right arm. Recovery occurred in a short time.

Forlanini reports a case of lung abscess in which artificial pneumothorax was attempted. The point of the needle had just been introduced into the pleura, when the patient developed a general convulsion followed by hemiplegia on the right side. Consciousness returned in a half-hour, but the paralysis persisted until the next day when it improved, leaving a monoplegia of the right arm. A second case of artificial pneumothorax is reported by him, in which a convulsive seizure occurred during a filling of 90 cc. of nitrogen gas. In twenty minutes consciousness returned, but a paralysis of the right arm remained which also disappeared after two hours.

Fisher (7) reports a case in which perflation of an empyema resulted in paralysis which disappeared two days later. Forgues (8) reports the case of a soldier, 22 years of age, who suddenly fainted while having an empyema cavity irrigated. The pupils dilated, respiration was suspended, the pulse was absent, and in five minutes consciousness returned but there remained a hemiplegia of the right side. Recovery from the paralysis was gradual and required about three hours.

Cordier (3) reported a case in a woman, 37 years of age, with a puerperal infection and cavity signs in the apex of the right lung. Exploratory puncture with a Luer syringe and lumbar-puncture needle delivered only a few drops of blood. The needle had barely been withdrawn when epileptiform symptoms developed, the face was deviated to the left and the eyes to the right; and bilateral clonic convulsions occurred, lasting one to two minutes, with a tonic phase for six to seven minutes. For two hours there was unconsciousness with later convulsions of the arm, and during the night death occurred.

Pisani reports a patient, 27 years of age, in whom the fourth refill of a left-sided artificial pneumothorax resulted in syncope, with mydriasis, convulsions and temporary hemiplegia.

The following case is reported because it presented many interesting sides and revealed symptoms which appeared to come under group 3 of Cordier's classification.

R. D., a female, single, 21 years of age, cashier by trade, came to Colorado from Chicago for her health four days prior to her examination on September 18, 1922. The family history proved unimportant. The previous personal history included measles in childhood. During March and August of 1919 she was a victim of two automobile accidents, but was not seriously injured. During 1919 she developed pneumonia. Since her pneumonia attack she had had cough and some expectoration, and for a period of over a year prior to coming to Colorado there occurred a marked increase in both of these symptoms. She noted also that she tired easily but was able to continue her vocation. In April, 1922, she developed pain in her right chest and began to feel weaker and more languid, and her appetite became poor but she did not lose any weight. In August, 1922, she had a moderate hemorrhage which was followed by slight fever lasting for three days. Soon afterward she left Chicago for the West.

Examination on September 18, 1922, revealed a general appearance of ill health. The patient's skin was pallid; she inclined to being stout; her weight was 124 pounds and height 5 feet, 4 inches; her cough was severe, especially in the morning; and expectoration was profuse. On moderate exertion she had dyspnoea and her appetite was poor, but her digestion was unimpaired. Her bowels were regular and sleep normal, there were no night sweats and her menstruation was normal. Her respirations were 22, pulse 120 and temperature 97° to 100.2°F.; her blood pressure was systolic 110 and diastolic 75. Inspection revealed depressions above and below the right clavicle, and cervical adenitis. On percussion there was impaired resonance from the third interspace and the fifth dorsal spine up, on the right. Ausculation revealed bronchial breathing and increased voice transmission in the upper part of this area. Moist râles, mostly fine, were present from the fourth interspace and seventh

dorsal spine up. On the left side there was a slightly impaired resonance above and below the clavicle and from the second dorsal spine up, with a few indeterminate râles heard in this area.

The sputum showed tubercle bacilli in moderate numbers. The urine was normal. Blood examination revealed hemoglobin 70 per cent, red cells 4,200,000 and leucocytes 6,800.

The clinical diagnosis was tuberculosis, pulmonary, chronic, moderately advanced, active upper and middle lobe of right lung, inactive apex of left lung.

The patient was sent to the Oakes Home, and placed on the customary treatment of rest and nourishing food. Her general condition improved somewhat, cough and expectoration became less and her temperature became normal although there was an occasional rise from 99.2° to 99.6°F. In March, 1923, she contracted a cold, consequent to which her cough and expectoration became worse and her fever returned. In May it was decided to collapse the right lung. No special difficulty was encountered in entering the pleural space. During the month of May she was given five fillings, in amounts varying from 350 to 600 cc. of air, at intervals of three days to one week. She was fluoroscoped during June, and only a partial collapse was found to be present and there were evidences of extensive adhesions. During June and July only two fillings were given, in amounts from 200 to 600 cc. of air. On August 14 some difficulty was encountered in obtaining proper manometric readings, and only 200 cc. of air was introduced as she complained of pain and feeling faint. On August 21 the patient was to have received her twelfth refill. The fourth interspace in the right midaxillary region was painted with tincture of iodine, and 0.5 cc. of a 0.5 per cent solution of novocaine in a 1 to 10,000 adrenalin solution was injected to render the introduction of the needle painless. This was the identical technique used in the eleven previous pnemothorax operations on this patient. After waiting about ten minutes a 20 gauge needle, connected by a rubber tube to a water manometer, was inserted in the prepared area. No manometric oscillations were obtained, and after three minutes of needle manipulation the needle was withdrawn and another point near the first puncture was selected and the needle reintroduced. The needle was manipulated for not more than a half-minute without obtaining any manometric oscillations, when the patient suddenly became unconscious, and developed a slight convulsion accompanied with frothing mucus at the mouth. The needle was quickly withdrawn and a hypodermic of 1/150 grain of atropine was administered. Her normal facial color was maintained during the convulsion, which was accompanied by involuntary urination. Artificial respiration was resorted to, although there was no cessation of the breathing and the pulse appeared fair in quality. In about three or four minutes the patient developed a complete paralysis of the left side of the face and the body, and the eyes deviated to the

right. In about twenty minutes she regained consciousness, and within an hour from the beginning of the attack the paralysis of the left side disappeared and the normal use of the side returned. During the attack the pupils were dilated; the patellar reflex on the paralyzed side was diminished, being almost absent; and the Babinski reflex was not present. The only unpleasant sequela of the attack was a violent headache over the right eye accompanied by vomiting attacks during the afternoon of the accident.

No further attempts were made to administer artificial pneumothorax and the patient at present, January, 1924, is improving, is ambulant, and has a normal temperture and a pulse rate of 72 to 84.

DISCUSSION

Whether, in the case reported, we are dealing with air embolism or hysteria, I am unable to decide. The absence of increased deep reflexes on the paralyzed side, the absence of facial pallor, the character of the pulse and the unchanged respiration would argue against a central lesion such as air embolism might produce. On the other hand, cases of unilateral paralysis followed by recovery have been reported in which air emboli have been demonstrated in the eye-ground, and in several instances in which death ensued air emboli could not be demonstrated postmortem, even though air emboli were seen in the eye with the ophthalmoscope, either just before or after death. It is, therefore, conceivable that an air embolus, evanescent in character, could have produced the symptoms in this case and the patient recover in the manner described.

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A PLEA AGAINST THE INDISCRIMINATE USE OF ARTIFICIAL PNEUMOTHORAX IN THE TREATMENT OF PULMONARY TUBERCULOSIS

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The treatment of pulmonary tuberculosis by artificial pneumothorax is now so well recognized that it seems almost heretical at so late a date to write concerning its indiscriminate use.

Many men, who profess to be experts in phthisiology, are using it so haphazardly and so thoughtlessly that great numbers of really suitable cases are being deprived of one of their best opportunities for complete recovery; while, on the other hand, many unsuitable cases are being put to useless, unnecessary and painful procedures. That this group of patients is large and so tends to discredit an acknowledged useful therapeutic procedure is, to say the least, deplorable.

The explanation for this state of affairs is not very easy. The giving of "gas" is in itself a relatively simple procedure (and in private practice quite remunerative) and requires very little surgical skill. But the knowledge of how to carry a case through successfully over a long period of time, the treatment of unavoidable complications such as fluid, rupture of adhesions, pleural shock and so forth, and the understanding of pressure relationships in the thoracic cavity come only after long experience and careful study and observation. I think that it is the ease with which pneumothorax can be performed that has made certain inexperienced and untrained men use it in a way that operates to the detriment of the treatment itself. That such practice is widespread is certainly beyond doubt, for I have personally seen numbers of patients coming from different sections of the country who have received pneumothorax treatment in a haphazard, careless fashion.

A brief case report of some of these cases, in order to bring out the incorrectness of the procedure and its indications, may not be amiss, and it is my hope to play some little part in checking the indiscriminate use of a life-saving therapeutic measure.

1. THE USE OF PNEUMOTHORAX TO CHECK HEMOPTYSIS

The most dramatic and useful results of induced pneumothorax are seen in cases of severe pulmonary hemorrhage, in which, after every other conceivable remedy has been tried, the pneumothorax controls the bleeding without any difficulty in almost spectacular fashion. Strange to say, it is in this group of cases that pneumothorax has been used most indiscriminately. When the treatment is used as an emergency measure in a patient who is otherwise unsuitable for continued pneumothorax the stopping of the treatment, once the emergency is over, is certainly indicated. But how about the patient with an extensive unilateral tuberculosis who first receives pneumothorax treatment as an emergency procedure to control hemoptysis? After the first four to six treatments bleeding is controlled and stopped, and at once the treatment is discontinued as no longer necessary. This group of cases is so large that I can cite at least one dozen cases in which this procedure used as an emergency measure worked to the detriment of the patient later on in the progress of his tuberculosis.

Case 1: H. L., age 25, duration of pulmonary tuberculosis four years. When first taken ill he was admitted to a sanatorium in Pennsylvania. Severe repeated pulmonary hemorrhages characterized his illness at that time. In one of these attacks he was given four pneumothorax treatments. Hemorrhage was controlled and gas inflations were discontinued. Several months later he went to Denver, and his clinical course in the next few years was marked by repeated febrile attacks, lasting several months at a time, which all the usual sanatorium methods seemed unable to control. Because of the distinct onesidedness of his lesion, pneumothorax was always considered but not given, since it had previously been resorted to in this case, thus making the chances of obtaining a suitable space rather remote. After two years of dilly-dallying, when nothing further could be done for the boy, pneumothorax was attempted and a relatively free, useful space was obtained, and the patient's clinical course changed to one of improvement, gain in weight, and cessation of symptoms.

The lessons to be learned from this case are obvious. When pneumothorax is used as an emergency measure in a patient who is otherwise suitable for the treatment, the latter fact alone should supersede the emergency and the patient should receive further and continued treatment as if no emergency had existed. In other words, an emergency occurring in such a patient should serve only to precipitate active measures which might otherwise have been delayed. Pneumothorax, once given and discontinued, only takes away from the patient the opportunity to use it in the future, should the need arise. This case also serves to illustrate the fact that pleural adhesions do not always form when pneumothorax is once given and discontinued, and one

should not hesitate to attempt pneumothorax again when indications are present. Riviere (1) cites various authors in confirmation of this point.

2. DISCONTINUANCE OF TREATMENT BECAUSE OF INABILITY TO COPE WITH COMPLICATIONS

The cases to be cited under this caption are really so elementary that I was surprised to find them in going over my case records.

Case 2: M. V., age 30, duration of pulmonary tuberculosis five and one-half years. His clinical course at all times was characterized by continued low-grade activity despite the absence of an advanced lesion. Under thorough rest his symptoms of cough, fever, hemoptysis and expectoration would disappear, only to return again with increased physical activity on his part. Physical examinations five years after onset disclosed a moderately advanced active pulmonary tuberculosis involving the right upper lobe with probable cavitation. On the insistence of the patient, pneumothorax was resorted to and after five or six treatments the procedure was abandoned because he had sudden severe hemoptyses. He was told that this was caused by the pneumothorax and that it was advisable to discontinue treatment.

Is there any need to comment on the incorrectness of the procedure adopted in this case? Had the operator had any training at all in pneumothorax, he would have known that to compress the lung further was the procedure *sine qua non*. Instead, he has made not only the patient, but all those about him, everlasting enemies of pneumothorax.

Case 3: S. G., age 27, duration of pulmonary tuberculosis four years. His clinical course before pneumothorax was characterized by excessive cough and expectoration, low-grade fever and at times colored sputum. Physical examination disclosed extensive infiltration on the left side, with a large thick-walled cavity occupying the greater part of the upper lobe. There were many moist râles over the right base. Pneumothorax was resorted to and a fair collapse was obtained on the left side. This was maintained for several months and, despite this, cough, fever and expectoration persisted. Fluoroscopy accounted for this by the fact that the cavity in the left upper lobe was firmly held down by adhesions and was at no time collapsed. About three months after treatment was instituted the patient suddenly began to run high fever and he complained of shortness of breath. This persisted for several weeks, when examination disclosed the presence of a pleural effusion accompanied by a probable spontaneous pneumothorax. The surprising thing, to the patient, was that after the severity of his symptoms had subsided his distressing cough and expectoration had absolutely disappeared. Pneumothorax was discontinued, and in less than two months the lung reëxpanded, bringing back with it the distressing cough and expectoration with almost all their old time severity.

When pneumothorax was, so to speak, in its infancy, many workers believed that, once fluid developed, continued treatment by refilling with air was no longer necessary, as the effusion served to keep the lung collapsed. All thoughtful workers are now agreed that the correct

method is to try to keep up the pneumothorax as long as possible. For, once the lung reëxpands following the absorption of fluid, numerous firm adhesions are formed and make collapsing the lung almost impossible in the future. In some few cases adhesions form rapidly, and obliteration of the pleural space takes place. It has been my experience that only in these cases can the pneumothorax be safely abandoned, as they usually do well, owing to the fibrosis and contraction that take place. Fishberg (2) makes mention of this fact. The literature on the management of pleural effusions in the course of therapeutic pneumothorax is so extensive that any one, who undertakes to treat a patient with it, should never be at a loss as to just what to do when this complication arises. A paper by Stivelman and Rosenblatt (3) is certainly worthy of mention.

3. THE USE OF PNEUMOTHORAX IN DISTINCTLY UNSUITABLE CASES

One cannot condemn too strongly the use of pneumothorax in distinctly unsuitable cases, in which no emergency exists to warrant it. Two case reports under this heading will serve to illustrate this point.

Case 4: J. H., age 40, duration of pulmonary tuberculosis three years. History points to an acute onset with probable tuberculous pneumonia. Following this, fever, cough, expectoration and hoarseness became constant symptoms. Physical examination, May 19, 1923, disclosed the presence of a far advanced, active, bilateral pulmonary tuberculosis, with extensive fibrosis and cavitation on the right side. Fluoroscopy showed the right diaphragm to be markedly retracted and adherent. Extensive ulceration and destruction of all the laryngeal structures was a complicating feature. About three months later the patient received five pneumothorax treatments on the right side although no particular emergency existed. The treatment was at all times most painful, due to the inability to obtain a suitable space, the patient herself describing it as more "painful than labor." Further injections were, of course, discontinued.

Case 5: M. C., age 31, duration of pulmonary tuberculosis over six years. Fever, cough, expectoration, continuous loss of weight and hemoptysis have been constant symptoms in the last two years. Physical examination disclosed the presence of a far advanced, bilateral, active pulmonary tuberculosis with extensive fibrosis and cavitation throughout the left lung. Laryngeal examination showed tuberculous infiltration and ulceration of the arytenoids, commissure and the left vocal cord. Some time later the patient received several pneumothorax treatments on the left side. They were soon discontinued because no apparent benefit resulted.

In both of these cases the only evident indication for the production of a pneumothorax was that the patients were hopelessly far advanced. They were both treated privately and, no matter how one looks at it, the monetary consideration involved cannot be put aside. Let us grant

that the operator could have obtained a suitable space in either of these cases, was not the uselessness of the procedure only too evident? · Pneumothorax carried out on such cases certainly does no good for the patients, except to bring them closer to the realization that nothing further can be done for them; and, as far as increasing the reputation of the treatment itself as a therapeutic procedure in the eyes of the general medical public, it serves, so to speak, only as a "knockout blow."

COMMENT

It is not the purpose of this paper to go into detail as to indications, treatment of unavoidable complications and management of cases over a long period of time, but only to call attention to the fact that such a condition as the indiscriminate use of pneumothorax by untrained workers does exist. The cases that have been cited are not exceptional or out of the ordinary. They have been carefully selected as typical of a large group that I have personally observed; and I would reiterate that such a state of affairs only tends to bring into disrepute a treatment the value of which has been proved beyond a doubt.

I have not meant to imply that the indiscriminate use of pneumothorax is limited solely to individual practitioners; it is also present to a large extent in many sanatoria. In one sanatorium, known nationally for its research work (on animals), pneumothorax is used extensively, but carelessly and thoughtlessly. It was my fortune at one time to see many of this sanatorium's cases after they had left the institution. The usual routine was to treat all patients on the pneumothorax roster once a week, regardless of whether it was necessary or not. Fluoroscopic examinations were only seldom done and to obtain a positive pressure was the sole object. One patient, so treated for one and a half years, never had any pathological condition in his chest, not to mention tuberculosis. To one it seemed as if an experiment was being tried on human beings, the only object being to see unusual things and the writing of "scientific" papers.

There are several other points that I would like to call attention to before bringing this paper to a close. The first is the use of fluoroscopic control in the treatment of patients by artificial pneumothorax. To my mind, this is one of the indispensable conditions under which treatment should be started. No man, no matter how well versed he is in the art of pneumothorax, should undertake to treat routine cases over

a long period without frequent fluoroscopic examinations available. Another very important consideration is the financial side of pneumothorax treatment in private practice. There is only one time when pneumothorax should be resorted to in a patient who is financially unable to carry out such treatment otherwise, and that is in the presence of a real emergency. It is the experience of most men doing tuberculosis work that hemoptysis, almost the only real indication for emergency pneumothorax, in the vast majority of cases will be overcome with very little active treatment. It is the duty of the physician, if he wants to do the right thing by his patient, to explain what pneumothorax means and to ascertain before treatment is commenced whether or not there are funds sufficient to carry out the treatment over a reasonable length of time. I could cite many a tragic instance when the physician failed in his duty in this respect and, had he referred the patients to the proper charitable institution, their chances for ultimate recovery would certainly have been better.

SUMMARY

1. Attention is called to the indiscriminate use of artificial pneumothorax in the treatment of pulmonary tuberculosis.

2. The practice of pneumothorax should be limited only to those men who have been thoroughly trained for this work.

3. Cases are cited to illustrate the incorrectness of the procedures used and the following points are brought out:

a. Pneumothorax, once begun in the presence of an emergency such as hemoptysis, should not be discontinued if the patient is otherwise suitable for pneumothorax.

b. When the indication is present, attempt at pneumothorax should be made, despite the history of use of it in the past.

c. Hemorrhage occurring during the course of pneumothorax treatment should only serve to make the operator continue the treatment by further compressing the lung.

d. Pneumothorax should not be discontinued with the onset of pleural effusion and all efforts should be made to keep the pneumothorax open as long as possible.

e. In certain cases following pleural effusion obliteration of the space takes place rapidly and only in these may pneumothorax be discontinued with any degree of safety.

f. The use of pneumothorax in distinctly unsuitable cases, in the absence of any emergency, cannot be condemned too strongly.

4. The use of frequent fluoroscopic control in the treatment of pulmonary tuberculosis by artificial pneumothorax is indispensable, even to those who are well trained in the art of pneumothorax.

5. Patients should not be treated with pneumothorax in private practice, outside of a real emergency, if they cannot afford to carry out treatment over a reasonable length of time.

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CONTROLLED DIAPHRAGMATIC BREATHING IN THE TREATMENT OF PULMONARY TUBERCULOSIS

S. ADOLPHUS KNOPF

In the *Transactions of the National Tuberculosis Association* for 1923 I have published an extended account of the development, to date, of my method of controlled diaphragmatic breathing. In this may be found a discussion of the physiological rationale of the method, as well as numerous comments which leading internists and phthisiotherapeutists, of both this country and abroad, have been good enough to make concerning its use and promise. With few exceptions these opinions have been favorable; and some, that have been based on trial and experience with the method, have been enthusiastic. I would refer the reader to the above mentioned publication for the views of those who have given the procedure some practice and attention. The present contribution is an abbreviated form of the paper in the *Transactions*, and is submitted here that certain essential details and particulars, which a larger experience with the method has brought out, may be brought to the attention of a wider circle of those interested in the treatment of pulmonary tuberculosis.

CONTRAINDICATIONS

The method may not be suitable for the far advanced case. A terminal case should be made comfortable by all possible means, and if controlled diaphragmatic breathing causes the patient physical or even only mental discomfort it should not be resorted to. There are also other contraindications, such as involvement of the lower lobes or such pleuritic adhesions to the diaphragm that diaphragmatic breathing is accompanied by pain. Pleuritic, intestinal or peritoneal involvements which cause pain with diaphragmatic breathing are, of course, also contraindications. Strange as it may seem, emphysema is sometimes relieved and sometimes aggravated by diaphragmatic breathing. The surest way is not to use it when it causes pain, or increases cough or discomfort.

During a recent consultation the question arose as to whether a complete or partial artificial pneumothorax is a contraindication to controlled diaphragmatic breathing. The answer is: When the patient can practice the method without pain, increased cough or distress, a complete or partial collapse is no contraindication. When at rest, in a recumbent position, the patient needs less oxygen for sustenance, and when the lower portions of both lungs are in fairly good condition dyspnoea will rarely accompany or follow diaphragmatic breathing. In most cases the collapse is usually confined to the upper and middle portions of the lungs. During this rest-breathing the lower portions of the lungs are doing the work and their better ventilation can only be considered beneficial.

With the contraindications just enumerated in mind, the treatment can easily be employed in all stages of the disease, except in absolutely terminal cases. Even in ordinary third-stage cases, when by patient teaching of the *modus operandi* the patient can be made to realize the advantages of the procedure, it is bound to do him some good and may relieve some of any distressing symptoms he may have. The only cases in which the treatment is really useless are those in which the patients are too lazy or too indifferent or, for other reasons, unwilling to carry out the instructions for reduced and diaphragmatic breathing.

The most satisfactory results from this physiological adjuvant in the rest cure of pulmonary tuberculosis may perhaps be obtained in a sanatorium or hospital where the patients have come, so to speak, to occupy themselves with getting well, unless the patient has "the sanatorium treatment at home" under careful medical supervision.

THE PHYSICIAN'S TASK

Before proceeding to describe the revised *modus operandi*, which I trust will make it easy for any physician to teach this method, I want to give just a few words of advice on the importance of entering into the right relationship with the patient when presenting a new method of treatment which does not at once show any startling result like some specific remedies; insulin in diabetes for example, or a successful artificial pneumothorax in pulmonary tuberculosis. The wonderful results which were obtained by such men as Brehmer and Dettweiler of Germany,

Daremberg and Sabourin of France, Walters of England, Saugman of Denmark, and Trudeau and King of our own country, have justly been ascribed and were no doubt largely due to their personal qualities, their charm of manner and their tact in dealing with patients.

Prior to artificial pneumothorax, rest and again rest, patience, resignation, implicit confidence in the physician and willingness to carry out his instructions were the essentials in the treatment of tuberculosis. With the advent of artificial pneumothorax another valuable remedy was added to our armamentarium. It can, however, only be applied in a very limited number of cases. So great an authority as Pottenger, in a recent discussion of the subject (1), wrote: "Pneumothorax should not be considered a cure for tuberculosis. I do not find it indicated except in a very small group of cases. Any patient who can get a result without pneumothorax is better off than one who has had his lungs compressed." Some clinicians are more optimistic about its results; but, be this as it may, it is now generally admitted that artificial pneumothorax cannot be applied as a routine treatment for pulmonary tuberculosis. It must be admitted, furthermore, that it is not indicated in early cases and that, as a whole, there are many more cases in which it is not applicable than cases in which it is. On the other hand, the method which I recommend is, with few exceptions, indicated in all cases of pulmonary tuberculosis. It is therefore my belief and has been my experience that, if a physician will enter heart and soul into this new therapeutic method—which might be called a substitute for artificial pneumothorax—and practice the diaphragmatic breathing himself before teaching it, so that he can inspire the patient with the hope that there is something which he can do to help himself get well, something that costs nothing and requires only patience and attention, the physician will surely be rewarded by seeing his patients getting better.

This will hold good for the family practitioner as well as for the sanatorium physician. Of course, the sanatorium physician has certain advantages; but the family physician may be equally successful, for here we have, more than anywhere else, the factor of the personal equation. The family physician, having the absolute confidence of his patient, and knowing his peculiarities and state of mind, can often accomplish a good deal more in cases in which the psychic and nervous

elements are involved than the institution physician. I have had private patients who became intensely interested in this rest-breathing, and they were soon rewarded for their efforts by a gradual diminution of distressing cough, fever and pleuritic pains. The more confidence and peace of mind and the more quiet and rest of body we can give the patient suffering with pulmonary tuberculosis, the greater will be our success.

Neither the number of patients in an institution nor its size should be considered a hindrance to the inauguration of the rest-breathing. Of course, there must be interest, if not enthusiasm, about it, on the part of the physician when he teaches his patient controlled diaphragmatic breathing. Once it is thoroughly instituted, the average patient will comprehend it, and an intelligent nurse can do the supervising after she herself has learned the method.

SOME PERSONAL EXPERIENCES

In the comparatively few cases which the consultant has an opportunity to observe for any length of time, I have met with decided success, some failures and some interesting experiences. One patient, after having been instructed in diaphragmatic breathing and told to breathe only superficially when he was not doing the controlled diaphragmatic breathing, insisted upon my seeing him again the next day with his family physician. On our arrival he complained bitterly of being miserable ever since he started the treatment because he feared to take a deep breath, and he longed to do so. All I could say was, "My good man take a deep breath whenever you want to." A little later his family physician informed me that since the patient had had the assurance that he could take a deep breath whenever he wanted to, he had lost the urge for it and was perfectly happy with the shallow breathing most of the time and to devote a few hours every day to the diaphragmatic breathing. Another case presented an interesting feature. His previous medical attendant had taught him deep respiratory exercises, using the costal and diaphragmatic muscles at the same time. He seemed to be unable to limit his respirations to the diaphragm but he could breathe superficially, using respiratory muscles only to a limited degree. When

allowed to breathe for a few days merely superficially, without paying any attention to costal or diaphragmatic breathing, he forgot about his previous respiratory exercises and, after three or four days, mastered the diaphragmatic breathing with perfect ease.

Concerning the influence of diaphragmatic breathing on patients who have a marked tendency to hemoptysis, I wish to relate the following experience: Two patients of mine who had bloody expectoration almost periodically every few months and who stated that it always lasted many days, assured me that this quiet and diminished breathing shortened the usual duration of their blood-spitting periods quite considerably. Of course, we all know that a hemorrhage or bloody expectoration may stop without any medication or other therapeutic means: general rest alone often suffices. Nevertheless, it is quite logical to presume that when the respiratory movements are diminished in number and the respiration restricted to the lower portion of the lungs rarely invaded by early tuberculosis, it may have a beneficial influence on the arrest of hemoptysis.

Lastly, there is good reason to believe that the frequent practice of diaphragmatic respiration will produce a hyperaemia in the upper invaded portion of the lungs, in which condition the tubercle bacillus cannot flourish.

COÖPERATION OF PATIENT

From the numerous letters received from sanatorium physicians and tuberculosis specialists it has become evident that when failures were reported they were usually due to lack of coöperation on the part of the patient. Some patients started with enthusiasm, but not seeing immediate results they gave up the method after a very short trial. For this reason every patient should be told that it may take some time before he can perceive any improvement, but that the method can in no wise be injurious to him, and that if he feels the slightest discomfort from it he should merely stop for the time. Other patients did not continue the rest-breathing, or used it irregularly or at altogether too rare intervals, because they forgot about it; some were naturally indifferent and did not care whether they got well or not.

It has already been stated that while rest-breathing may not prevent a hemorrhage, it surely cannot be the cause of one and has rather a tendency to lessen its severity and duration. When it happens, as in one case reported to me, that a patient has a hemorrhage after starting the rest-breathing, he will surely believe the hemorrhage was the result of his diaphragmatic respiration. He will then be afraid to continue it, and if he happens to be an inmate of a sanatorium, he will be likely to prejudice other patients against the procedure. It is therefore very important to explain the objects and aims and the safety of the procedure to the patient most particularly, and above all the necessity of his earnest and intelligent coöperation.

To make rest-breathing more interesting to the indifferent patient, he may be told to write down the number of diaphragmatic respirations he has taken per minute and the number of minutes he has persisted in the procedure, and then calculate at the end of the day how many respirations he has saved his lungs by having breathed only 6, 7, 8 or 10 times a minute instead of 20 or more times, whatever the number of respirations prior to beginning the treatment. Of course, he cannot do this without having a timepiece. If there is no clock where he can easily see the dial, a small clock or watch should be placed on a stand near the bed or suspended nearby, so that the patient will not have to tire his arm or hand taking out a watch every few minutes. If he succeeds in reducing his respirations from 20 to only 10 per minute and, by periods of several minutes' rest-breathing, arrives at a total of 5 hours, he will have saved his lungs 3000 respirations, or 6000 movements. Let him also bear in mind that by this physical and mental rest his pulse will become slower and his heart more quiet, and that this rest-breathing cannot possibly harm but can only benefit his general condition. Thanks to the courtesy of the Mayo brothers and Dr. Walter M. Boothby, their chief of the metabolic service, it was my privilege, during a recent visit to the Mayo Clinic, Rochester, Minnesota, the "Mecca" of American surgery and medicine, to have some metabolic tests made in connection with my method of rest-breathing. These tests proved that there was a difference of less than 0.5 per cent between the intake of oxygen and giving out of carbon dioxide under the two

conditions; that is to say, during normal and during controlled diaphragmatic breathing. The change in the basal metabolic rate was from + 3 to + 1, which, as Dr. Boothby says, is without significance. The respiration was reduced by half during the controlled diaphragmatic breathing and the pulse rate 3 per minute.

The patient should be made to understand the necessity of shallow breathing when he is not using the slow diaphragmatic method, and of course he should never cough unless he feels the necessity of expectorating. It goes without saying that just as the general rest cure must always be carried out where the air is fresh and pure, so should it be with the rest-breathing. In cold weather the feet should be warmed with the aid of hot-water bottles or bags, and in summer a comfortably cool place should be chosen. If there is sunshine, the patient must place his reclining chair or bed so that his head is in the shade. It is best not to resort to the slow breathing until an hour or an hour and a half after a heavy meal.

The tuberculous invalid should be impressed with the fact that, if he has the good will, patience and perseverance to carry out the rest-breathing method conscientiously and in a cheerful and hopeful frame of mind, he will surely derive great benefit from it, and it will lead him toward a more rapid recovery. Whenever sad or depressed thoughts come over him, he will easily dispel them by concentrating his mind on diaphragmatic and restricted breathing, something which he himself can do toward bringing about his own recovery.

ADDITIONAL MEANS

Except shortly after hemorrhage, or as long as the patient still has sanguineous expectoration, he should be encouraged to drink plenty of pure water, preferably slightly alkaline, at least six to eight tumblerfuls per day, between mealtimes. Those who follow this order are usually better able to reduce their respirations than those who neglect carrying out the instructions to drink plenty of water. If the patient is afebrile, a daily fairly vigorous massage of the upper and lower extremities and a light massage over the chest, abdomen and back will be of considerable

benefit in overcoming the tendency to muscular degeneration from prolonged rest.

The patient should be impressed with the necessity of sleeping on the affected side, so as to inhibit the respiratory movement of the diseased and inflamed lung as much as possible. Of course, in exceptional cases it may be helpful or even necessary to use restrictive appliances such as Sewall's belt (2), adhesive straps (3), plaster of Paris trough or cast (4), Stewart's splint (5), or the pneumatic chest-splint (6) in order to help obtain the desired rest for the invaded portion of the lung. Nevertheless, no matter what mechanical means are used to restrict breathing in the upper portion of the lungs, the patient should first be taught the method of controlled diaphragmatic breathing. If he has grasped the idea, even if the performance is difficult at first, the diaphragmatic breathing will materially help him when wearing the restrictive appliance.

Webb's postural treatment may well be added, as a help to procure rest for the afflicted lung during sleep or even during the day. Besides urging the patient to sleep on the affected side, Webb places under the dependent side a small firm pillow to restrain the motion of this lung to a greater degree (7). Sometimes a simple flannel or muslin bandage, pinned so that it can be easily removed if the patients, especially those in the advanced stages of the disease, experience a feeling of suffocation, may be put around the upper portion of the thorax to help in teaching how to limit breathing to the lower lobes. When in the recumbent position a hot water bag, or a bag filled with sand or small shot, resembling a saddle-bag and weighing from a half to five pounds, according to the size of the chest and the condition and strength of the patient, may be placed across the sternum and will often answer the same purpose. When resting or sleeping on the affected side, the motion of the chest may be still more restricted by placing the sand or shot bag so as to straddle the well or relatively well portion of the chest. This will serve as an additional rest measure for the inflamed lung. An electric heating bag, properly regulated so as not to burn when the patient falls asleep, may be resorted to, in order to relieve intercostal neuralgia or other vague pains in the chest. If it is desirable to produce a heavier weight than

the electric pad represents, so as to compress the chest, a bag of sand or shot may be added. A hot-water bag would have to be especially constructed so that it would be placed astride the side of the chest.

MODUS OPERANDI

The best position for the patient to assume, when being taught the practice of controlled diaphragmatic breathing, is to lie in or on the bed or on the reclining chair in a semireclining position, with feet extended and slightly separated, a position which demands the least cardiac effort against gravity. This position can be best obtained in bed by the use of three or four pillows, and later on it may be imitated as closely as possible on the typical sanatorium reclining chair, by regulating the back of the chair so as to be at an angle of 30 degrees. In this position relaxation is most easily obtained and the heart is called upon to do the least work. It goes without saying that, if the patient is dressed, there must not be any garments that would restrict the free exercise of the diaphragm and abdominal muscles.

Before beginning the rest-breathing it is presumed that, as the result of the explanation and instructions given him beforehand, the patient will be relaxed in mind and body. This relaxation of the body is essential, and whatever muscular effort is exerted during the breathing exercises should be as slight as possible. He is then told to imagine that the respiratory movement begins in the toes of the right foot, the inhalation gradually traveling upward as far as the diaphragm on the right side, then crossing over to the left, and gradually descending during exhalation downward to the left foot. While, of course, this breathing upward from the toes to the abdomen is merely imaginary, it results in a diaphragmatic breathing, and whatever quantity of air is inhaled passes mainly through the lower portions of the lungs while the upper portions, where tuberculous lesions are usually located, are put, if not at complete, at least at comparative rest.

The patient must, of course, concentrate his mind on this procedure. He cannot and should not be thinking of anything else during this rest-breathing period. The surest way to teach the procedure correctly is to ask him, during inhalation and during exhalation as well, to follow the

physician's hand with index finger pointing, as it moves, in the upward direction from the right toe and over to the left side of the diaphragm, then downward to the left foot. When the physician's finger has arrived at the left side of the diaphragm it will pause, while the patient may hold his breath a second or two and then exhale during the downward movement of the finger. The relation of the duration of the two acts should be 5 for inhalation and 4 for exhalation. With some patients ten seconds may be spent for the cycle, 5 for inhalation, 4 for exhalation, and 1 for pause between inhalation and exhalation. With other patients, particularly the more advanced cases, it may be necessary to count rapidly and shorten the cycle. Nearly all cases are able to lessen the number of respirations per minute with absolute comfort by stopping after the exhalation two, three or more seconds before inhaling again. In fact, one may leave the duration of the interval between each cycle of the respiratory movements to the ability of the patient to remain quiet before inhaling again. If he is able to hold the air after inhalation several seconds longer, he may also do so.

It will often be necessary to repeat this rest-breathing procedure several times before the patient has fully grasped the *modus operandi* and does it correctly. A good way for the physician to assure himself that his patient has fully mastered and understood the rest-breathing is, while indicating the direction and duration of the inhalation with one hand, to place the other over the upper portions of the lungs, and thus observe whether they are at complete or at almost complete rest, and with his eyes fixed on the abdominal region see that the diaphragm does its work properly. Later on, by placing his own hands, one on his chest and the other on his abdomen, the patient may learn to know whether or not he is doing the diaphragmatic breathing correctly and giving the upper portion of the chest the desired repose.

Before leaving the patient, the physician should count the number of respirations per minute with watch in hand, and thus see what can be accomplished. This is particularly indicated with highly nervous and dyspnoeic patients, who must be shown what can be achieved with patience and perseverance in the reduction of respiratory movements. This class of patients take many short, jerky breaths per minute and

seem to have no control over their diaphragm. They must be assured that they will learn with practice, and they may begin by stopping a few seconds after exhaling, which is the easiest part of the procedure. This mastered, they will learn to stop also a second or two after inhalation and learn the use of the diaphragm.

We will now consider when and for how long a time, and how often, the patient should resort to this slow and controlled diaphragmatic breathing. If the patient is a bed case, he may be told that, since it cannot do him any harm and that with every additional minute of rest he gives his lungs his condition is bound to improve, he should do it whenever he feels like it, and as long a time as he enjoys it. It is rare that the patient, particularly at the beginning, can keep up this rest-breathing continually for more than about 15 minutes. Some can do it for only 5 or 10 minutes at a time, but, as a rule, after an interruption of a few minutes, they can resume it for the same or a longer period. It does not tire them physically, but before the diaphragmatic breathing has become automatic it may have required a good deal of thought, concentration and frequent interruptions.

When the patient feels the need to take a deep breath he should not be afraid to do so. Ambulant patients, who are up and about but still taking the cure, should do the rest-breathing whenever they can, particularly in the morning after awakening, during the day when having their rest hours, and in the evening before going to sleep. Ambulatory and afebrile patients who, for one reason or another, are obliged to work, might take the rest-breathing when in a sitting position and in some instances may be able to do it without interfering with their work, and of course above all in the morning before rising and in the evening, after having retired. This breathing may also be practised at night if a patient is wakeful. In many cases, if done quietly and regularly, it will be found conducive to sleep.

When, in addition to the restricted respiratory movements, the patient trains himself to cough only when the accumulation of pulmonary or bronchial secretion demands it, he will be doubly benefited. The suppression of the so called dry cough may not only be relatively easily accomplished by will power, but it may be materially facilitated by

resorting quickly to diaphragmatic respiration. Experience has shown that diaphragmatic breathing, after being practised for a length of time, will become automatic and thus be of continued benefit to the patient until the complete arrest of the disease is accomplished and may even protect him from the danger of a relapse.

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ADDRESS OF THE PRESIDENT[1]

LIVINGSTON FARRAND

Ladies and Gentlemen: It is with a sense of very real privilege that I open officially this twentieth annual meeting of the National Tuberculosis Association. One welcomes, or should welcome, at any time an opportunity for a review of progress and method; and the close of a second decade of intensive effort seems to offer an especially appropriate occasion for an introspective survey.

It is quite inevitable that our minds should be turned to-night to a comparison of our results with the forecasts of twenty years ago and of the methods now employed with those tentative essays in an unexplored field which were put in operation in 1904. It was a historic step which resulted from the first meeting of a far-seeing group, for the National Association for the Study and Prevention of Tuberculosis has not only accomplished much in its own domain but has been a notable factor in stimulating similar organized efforts in related fields, until there has been brought about a nation-wide movement for the building up of the people's vitality which offers the greatest promise.

When the Association was first organized the underlying idea was undoubtedly that by intensive educational methods the American people could be informed of the prevalence and the dangers of tuberculosis and the methods by which the disease could be prevented. It was hoped that a sufficient number of sanatoria and hospitals could be constructed for the treatment and care of all patients affected with tuberculosis. It was hoped that, by scientific research, a definite cure might be discovered and that the whole tuberculosis problem might be solved in a relatively brief time.

In 1904 many of us felt that our knowledge of tuberculosis was very nearly complete. As we look back over the past twenty years, we cannot fail to realize that it was our ignorance that approximated completeness and that the striking fact has been the successive increases of knowledge with the consequent changes in the antituberculosis program. In 1904

[1] Delivered at the Twentieth Annual Meeting of the National Tuberculosis Association, Atlanta, Georgia, May 6, 1924.

it was generally known that tuberculosis was caused by the tubercle bacillus, that it was a communicable disease, that infection was brought about by the inhalation of the bacilli and that this infection was most frequently seen in crowded homes and particularly in the congested tenements and quarters of our large cities. The fact that infection usually took place in childhood was not accepted nor was it generally understood that infection from tuberculosis might take place without causing active disease. As early as 1892 Loomis of New York had demonstrated that when autopsies were made on individuals who had died from accident when in apparent good health, tubercles were frequently found and that when the material from these tubercles was injected into small animals, active tuberculous disease was induced. Naegeli had also found that over 90 per cent of the autopsies performed in a general hospital on persons dying at all ages revealed evidences of healed or active tuberculosis and suggested that everyone becomes more or less tuberculous before death, a substantial proof that infection may occur without active disease. In 1903 Von Behring made the flat statement that in all likelihood tuberculous infection commonly occurred in childhood and remained dormant until the disease was lighted up by some acute disease, overwork or other cause.

The statements of Loomis, Naegeli and Von Behring were not generally approved or, at least, their implications were not recognized. With the generally accepted facts of the situation at that time it seemed perfectly possible to destroy all bacilli at their source by giving instructions to tuberculous patients in their homes and by preventing expectoration in the streets and public places. The number of tubercle bacilli would immediately become less and the chances of becoming infected would be immediately diminished. The Association, therefore, urged the adoption of ordinances to prevent expectoration in public places, and it was urged that tuberculosis be generally made reportable so that health officials would be able to give the advice necessary to patients affected with the disease. With this same idea in mind the Association and physicians generally believed that it would be possible to construct a sufficient number of sanatoria and hospitals so that every patient affected with the disease might be isolated, as was urged by Newsholme and Biggs, and that those in whom the diagnosis was made early enough might be cured of the disease. These ideas resulted in a rapid increase in the number of sanatorium and hospital beds and in special dispensaries, in order to provide for the early detection of the disease. Tuber-

culosis nurses were employed to give instruction to the patients in their homes and to secure admission to hospitals and sanatoria for such patients as were in need of such care. Nearly everyone was satisfied with this campaign, to which was added the educational propaganda which was extensive and which was largely increased after the International Congress on tuberculosis in 1908, influenced by a remarkable exhibit on tuberculosis shown at that Congress. A similar exhibit had been prepared two years earlier by our own association and demonstrated to thousands of people by Mr. E. G. Routzahn in the principal cities east of the Mississippi. Later an exhibit was shown in every state west of the Mississippi by Mr. W. L. Cosper of the Association Staff. These exhibits gave an enormous stimulus to the antituberculosis campaign.

There have been certain changes in method during the last six or seven years due to the increase of our scientific knowledge. The discoveries of Loomis, Naegeli and Von Behring were slow in being accepted, but when Pirquet gave us the simple tuberculin test in 1907 physicians in general began to accept the idea that nearly everyone was infected with tuberculosis, that such infection took place in childhood and that as each year of life passed a larger proportion of individuals in civilized countries were infected with the bacillus. We then began to realize that there was a marked difference between infection and disease and that nearly everyone became infected with tuberculosis by the age of twenty, but that only a certain proportion of these people became actively diseased. This point of view has been of very great significance and has brought about a change in the method of attack on the tubercle bacillus. The efforts to cure the adult patient and to prevent the dissemination of the tubercle bacilli from sick patients were continued, and an active campaign for the care of children who were underweight or undernourished and to provide preventorium care for them was undertaken. Further, it was found that almost equally good results could be obtained for delicate children by providing open-air schools or open-air classes, by extra feeding and by more careful supervision, by providing summer outings for them and by endeavoring to instruct the parents to care for the child in such a way that it would not develop tuberculosis. These measures were taken primarily to help the child who was definitely undernourished and who had been exposed to tuberculosis or what is now generally known as a "contact." In 1916 the Association conceived the idea that not only should the undernourished child be cared for but also that a serious effort should be made to improve the health of all children.

A very ingenious plan was thought out by Mr. Charles M. DeForest which is now familiar to all of you—a plan known as the *Modern Health Crusade*. Without dwelling upon the details of the Modern Health Crusade I wish to emphasize the fact that it is a direct attack upon perhaps the most important problem now confronting us, namely, the establishment of sound individual health habits in the children of the country.

Unfortunately, there exists no agreement among authorities in pedagogy as to the best way in which this end can be attained, and much remains to be worked out as to method. There can be no doubt, however, that the Modern Health Crusade has made a striking contribution and that in coöperation with the other national agencies working in the field, notably the Junior Red Cross and the American Child Health Association, a proved and accepted method will ultimately be achieved and universally adopted in our schools. I need not say that I heartily approve the recommendations made by the Managing Director and the Executive Committee, looking toward the extension of health education for all classes of the community. This remains, as it has always been, a primary function of the National Association.

We have also a very striking contrast between the organizations that were available to combat tuberculosis twenty years ago and those that are available for this important work to-day. In 1904, if my recollection is accurate, there was a state association in Pennsylvania and perhaps a score of local societies scattered through the country. These few associations prior to the creation of the National Association represented the only voluntary efforts that were being made to combat tuberculosis. A number of health departments had already shown some evidence of leadership and in particular the Health Department of the City of New York which, under the direction of the late Dr. Hermann M. Biggs, had made more progress and taken more fundamental steps looking to the eradication of this disease than any other city in the world up to that time. To-day we find an association actively engaged in fighting tuberculosis in every state in the Union and over 1,350 local associations. Practically every health department takes special cognizance of the problem, although it must be admitted that in many of them the provision made for meeting the situation leaves much to be desired. The various state and local associations were organized either by the National Association or through the leadership of individuals within their own territories. These voluntary associations have been an all-important

factor in the antituberculosis campaign and I cannot commend too highly the activities which have been carried on by them. In this connection I wish to pay a special tribute to a group whose services are not always recognized. The brunt of the work of a voluntary association is borne by its executive, and it is to the executive secretaries of these associations that the greatest praise is due for having so effectively carried on the work of their societies. It is matter for congratulation that in nearly every state in the Union there is now an organized health department, an institution for the care of tuberculosis patients, that most of our larger cities have accommodations for advanced cases of the disease, that the number of dispensaries and tuberculosis nurses has mounted steadily and that provision for the care of children has increased especially during the last decade.

This marked progress has been possible because we have been able to raise an almost constantly increasing sum of money each year for the voluntary associations. The fund-raising campaign focuses the attention of the people on the tuberculosis problem. Searching questions are asked, and the public support given to the movement has been the greatest factor in stimulating appropriations by official bodies for the construction and maintenance of sanatoria, hospitals and dispensaries and for the employment of physicians and nurses.

The method employed in the fund-raising campaign is familiar to all of you. Launched first in 1907 in Delaware by Miss Emily Bissell, under the name of the Red Cross the seal sale netted $3,000. Since that time the total sum has largely and steadily increased and in 1923 was over $4,000,000. The sums raised in the various communities are usually well expended but here I feel that I must sound a note of caution. Fund raising should always be based on a sound program of active work. Experience has shown that surpluses, except in very moderate amount, are demoralizing and unwholesome. Seal-sale funds should not be set aside from year to year and husbanded for some expensive construction project.

In appeals for funds, definite sums should be asked for, based on a definite budget for a program approved by the local association. Overzealous executives should not take advantage of prosperous times and their good salesmanship to raise money for enterprises of doubtful value, nor should associations be forced to speculate on various uses for their funds after the returns are complete.

The executive should see to it that his budget is approved and that expenditures do not exceed income. Associations should neither run into nor remain in debt.

Sound finance and accurate audit are a source of strength in our associations. The program should be tested, its cost of application determined, the budget approved, needed funds secured, resources husbanded, accurate audits made and thus confidence obtained by giver and administrator.

In a large number of our cities a new method of financing the local social-welfare agencies has developed and is known as the *Community Chest.* The community chest or financial federation endeavors to raise funds for the support of all social agencies and requires each agency to submit a request for funds with a program of work and budget for the ensuing year.

This method is somewhat in conflict with the seal-sale campaign and frequently creates difficulties for the executives of the state and local tuberculosis associations. I believe that we should make every effort possible to maintain a seal sale on account of its educational value, and if that is not possible we should at least make use of this educational device by such distribution and accompanying information as may be available.

A newly formed or even an older community chest will not as a rule make an appropriation for a tuberculosis association based on its previous income from the sale of seals. The association will be compelled to submit a careful program and itemized budget and the executive must be prepared to explain and support every part of that program and budget. This is sometimes a trying task but it has its wholesome aspect.

The registered device, the double-barred cross, belongs to the National Association and this has been the medium through which the seal-sale campaign has become so successful. The National Association now grants its use to its directly affiliated associations which act as its agents in accordance with the annual contract signed by the national with the various associations. The National Executive Office endeavors to render to the agents every possible service it can with the means available, subject to the general policies laid down by the Board of Directors and Executive Committee.

The present system of representative directors is working well, though such a system in a country as vast as ours cannot be perfect. It is, however, democratic and correct in principle. Yet the Board, consti-

tuted as it is, cannot, with its meetings necessarily infrequent, define specific needs of service. The Executive Office, however, endeavors to sense these needs through intimate contact with state and local executives, either through small advisory committees or larger meetings. This mutual interchange of opinion and this balance between the Board, the Executive Committee and the National Executive Office have brought about a uniformity of purpose, to the mutual understanding and advantage of the entire group of tuberculosis associations.

These problems of organization are important but should not be unduly magnified. There is no question that at times too much thought and energy are expended on such abstractions as by-laws, rights and authority to the detriment of effective work.

Without organization, however, little progress can be made and, directly and indirectly, the organizations have played a very large part in reducing the death rate from tuberculosis in this country.

Each year we have seen improvement and each decimal point less in the mortality rate means so many fewer deaths, so many fewer patients, so much less suffering and anxiety and so much less economic loss. For these gains we are grateful and we hope that the end of the next twenty years will find us much nearer the final solution of the problem.

We must, however, frankly recognize the fact that in tuberculosis, as in other communicable diseases, there are many agents which play a part in their reduction or increase. We know that there are biological, economic and other factors which, interwoven with the great complexity of our modern life and civilization, exert an influence which is impossible accurately to estimate. There is a group of individuals who firmly believe that the death rate from tuberculosis was declining as rapidly prior to the antituberculosis campaign as it has since its inception. These individuals hold that the chief cause of the decline is the actual inheritance of the individual and that if no attempt had been made to combat the disease the diminution would have been just as rapid. There are others who believe that the economic factor plays the most important part, and from that point of view it is the food supply which claims first attention and that the increase or reduction of the death rate from tuberculosis depends largely upon the amount of food available for the masses of the population. To substantiate this they point to the experience in Europe where the death rates have increased enormously from tuberculosis in times of food scarcity and have diminished in turn in times of plenty. We have also noted as a result of careful studies

made by our own tuberculosis organizations of the comparative death rates from tuberculosis in different sections of the country, of the same state or in different localities in a large city, that there is a variation in the death rates of over 1000 per cent. In the sections of cities where living conditions are of the best it is not uncommon to find death rates from tuberculosis as low as 25 per 100,000 while, on the contrary, in the poorer districts where the families live in overcrowded conditions, and where a low standard of living exists with every opportunity available for infection, the death rates will run as high as 400 to 600 per 100,000.

We should look these facts in the face, consider them carefully and try to find new ways of ascertaining, if possible, what the exact factors are which play such an important part in bringing about the development of the disease tuberculosis, once infection has taken place. We must also face the fact that in some states and cities, where little or no effective antituberculosis work has been done by the health departments or by the voluntary agencies, a reduction in the death rate has taken place similar to that where the official and voluntary machinery has been most active and effective. In order to learn more of these problems the National Association appointed a special Committee on Medical Research several years ago which is engaged in considering and encouraging scientific investigations by qualified workers in special fields. An inquiry has recently been made as to the amount of funds and the number of workers available and it is known that in six different laboratories upwards of $200,000 annually is being expended on tuberculosis research with not less than 25 highly skilled technical workers. In a recent presidential address before this body Dr. Webb pointed out the need of further research in tuberculosis, emphasizing what knowledge had already been gained and indicating the obvious gaps in that knowledge. Laboratory and clinical studies since that time force us to accept the fact that we are far from knowing all that must be explained about tuberculosis, its causes, its treatment and its methods of prevention; nor can we wholly and satisfactorily explain the diminution of the death rate. On the other hand, we may heartily congratulate ourselves upon certain demonstrable facts. First, that an individual affected with tuberculosis at the present time has an excellent chance of cure and that this apparent cure or "arrest," if you prefer, will be permanent in most instances if the mode of life of the patient is properly directed.

We know, as Dublin told us last year, that the sanatorium has been most effective in prolonging the life and economic usefulness of large

numbers of persons. We know that tuberculosis from a humanitarian standpoint is better understood and that there is a greater aspect of hopefulness in the homes of the poor, where the disease most frequently occurs, than has ever been known before. We know that the death rate has been diminished by one-half. We know that gains are being made everywhere in the death rate from nonpulmonary tuberculosis hand in hand with the dimunition of the death rate from the pulmonary form. We know that during these past two decades there has been a steady prolongation of life at each age period until the average age of death to-day is 55 where twenty years ago it was only 48. That our National Tuberculosis Association and its affiliated societies have had a very large part in these notable gains, there can be no legitimate doubt.

One closing word as to the future. Each succeeding year of experience has shown how inextricably our campaign against tuberculosis is tied up with every other movement for the prevention of disease and the improvement of the public health. So true is this that it is inevitable, if our accumulated energy and resources are to be given their fullest expression, that there must be a frank modification of program and an enlargement of activity. This must be done, and done only, in fullest coöperation with the other national organizations which are striving toward the same end and which are now associated closely with us in the National Health Council. It is a splendid record of public service which these twenty years have written for our Association and I predict no less notable a contribution in a broader field in the two decades to come.

THE VALUE OF THE TRUDEAU SANATORIUM'S FIVE DIAGNOSTIC CRITERIA OF PULMONARY TUBERCULOSIS IN NEGATIVE DIAGNOSES

A STUDY OF 264 CASES ADMITTED TO THE SANATORIUM, DIAGNOSED AS NONTUBERCULOUS AND FOLLOWED UP FROM ONE TO SEVEN YEARS

LAWRASON BROWN AND FRED H. HEISE

Many of the negative diagnoses made at the Trudeau Sanatorium have recently been called into question elsewhere. An attempt has therefore been made in this paper to estimate the correctness of such diagnoses as based on the criteria worked out at the Trudeau Sanatorium.

In a previous paper (1) statistical data were given substantiating the belief in the value of these five criteria of diagnosis, which are as follows: (1) the history of an hemoptysis of a teaspoonful or more, (2) the occurrence of pleurisy with effusion, (3) the presence of persistent moderately coarse râles in the upper half of the chest, (4) a definite parenchymatous X-ray lesion of a tuberculous character in the upper half of the chest and (5) tubercle bacilli in the sputum. Neither the hemoptysis, especially when small, nor the pleuritic effusion should have occurred during an epidemic of acute respiratory disease, nor be obviously the result of some other cause. The râles should have an underlying parenchymatous X-ray change of a tuberculous nature.

In another paper (2) were presented statistical data on the value of the absence of a constitutional or focal reaction, as seen in the X-ray, after the subcutaneous administration of a repeated dose of 10 mgm. of old tuberculin. Briefly, it may be stated as our belief that, when a patient has no definite evidence of pulmonary tuberculosis and has no tubercle bacilli in his sputum and, in the absence of contraindicating conditions prohibiting the test, he fails to react to tuberculin given in the manner stated, a negative diagnosis of pulmonary tuberculosis can safely be made. When the X-ray evidence of tuberculosis is slight and contraindications to the test are absent, an increase of shadow (congestion) around the focus, as seen in the X-ray plate, and following

reaction to the test, should lead to a positive diagnosis and should indicate potentially active disease.

When none of the five criteria was present, pulmonary tuberculosis was said to be excluded. When an hemoptysis occurred under the conditions mentioned, or when a pleuritic effusion occurred as stated,

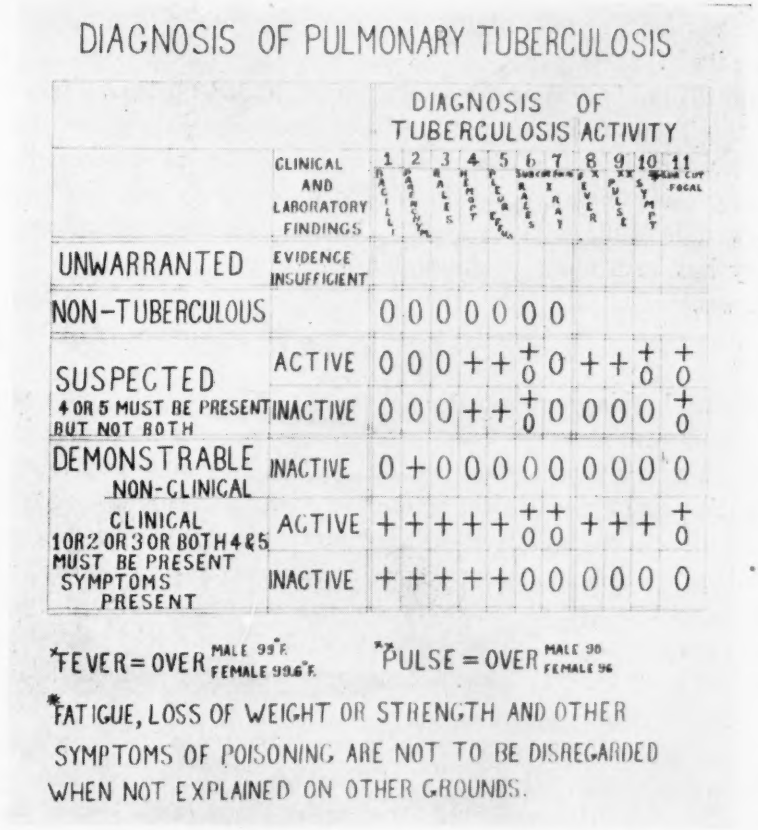
DIAGNOSIS OF PULMONARY TUBERCULOSIS
DIAGNOSIS OF TUBERCULOSIS ACTIVITY
CLINICAL AND LABORATORY FINDINGS
1 2 3 4 5 6 7 8 9 10 11
UNWARRANTED
EVIDENCE INSUFFICIENT
NON-TUBERCULOUS
SUSPECTED
4 OR 5 MUST BE PRESENT BUT NOT BOTH
ACTIVE
INACTIVE
DEMONSTRABLE
NON-CLINICAL
INACTIVE
CLINICAL
1 OR 2 OR 3 OR BOTH 4 & 5 MUST BE PRESENT
SYMPTOMS PRESENT
ACTIVE
INACTIVE
*FEVER = OVER MALE 99°F. FEMALE 99.6°F.
**PULSE = OVER MALE 90 FEMALE 96
*FATIGUE, LOSS OF WEIGHT OR STRENGTH AND OTHER SYMPTOMS OF POISONING ARE NOT TO BE DISREGARDED WHEN NOT EXPLAINED ON OTHER GROUNDS.

CHART 1. THE FIVE DIAGNOSTIC CRITERIA AND THEIR SIGNIFICANCE IN THE DIAGNOSIS OF CLINICAL ACTIVITY

and no further evidence could be found, a diagnosis of "suspected" pulmonary tuberculosis was made. When both occurred, a positive diagnosis was made. Râles not substantiated by X-ray or other evidence called only for a diagnosis of "suspected" pulmonary tuberculosis. A parenchymatous X-ray, when unaccompanied by symptomatic evidence of activity of the disease, led to a diagnosis of "nonclinical" pul-

monary tuberculosis. Tubercle bacilli found in the sputum only before entrance to the Sanatorium, and not corroborated by evidence of disease such as physical signs, X-ray, hemoptysis or pleuritic effusion, led only to a diagnosis of "suspected" pulmonary tuberculosis.

Subjective symptoms, such as elevation of temperature, increased rapidity of pulse, gradual loss of weight, fatigue and languor, were used as a basis for diagnosis of the activity of the disease and not of the disease itself.

From 1916 to 1923 approximately 2,000 patients have been discharged from the Trudeau Sanatorium. Clinical pulmonary tuberculosis was found to exist in 1,725 and nonclinical pulmonary tuberculosis in 11. The diagnosis remained somewhat in doubt in 61 and a negative diagnosis was made in 203. An analysis of these cases and of their subsequent history has been made to determine in a way the correctness of the diagnoses.

1. THE NONTUBERCULOUS GROUP

Included in this group were the following: one case each of pulmonary abscess, frontal sinus infection, bronchiectasis, periapical infection of all teeth, ovarian cyst, renal calculus, nephritis, gall stones, post-poliomyelitis paralysis, arthritis deformans with psoriasis, probable Raynaud's disease, rheumatism with purpura, mitral regurgitation, endocarditis, tonsillitis and tuberculous tonsils removed previously; 2 cases of malignant tumor of the lung: 4 of enteroptosis (relieved by belt, etc.); 4 of syphilis; 5 of thyroid disorders; 12 of bronchitis; 13 post-influenzal; 21 with various nervous disorders; and 126 in which disability was not diagnosed.

Temporary râles were heard as follows: *1. Moderately coarse at an apex;* in one case of "thyroid," 3 of "nervous disturbances" and 3 with "disability not diagnosed." *2. Moderately coarse in the central portion of a lung;* in 1 case of "post-influenzal disability." *3. Moderately coarse at a base:* in 4 cases of bronchitis, 3 of "post-influenzal disability," one of "nervous disturbance," one of bronchiectasis and 6 with "disability not diagnosed." *4. Moderately coarse at an apex and a base:* in one case of endocarditis and one of bronchitis. *5. Fine at an apex:* in 2 cases of "enteroptosis," one of "nervous disorder" and one with "disability not diagnosed." *6. Fine at a base:* in one of syphilis, 2 of bronchitis and four with "disability not diagnosed." *7. Fine at an apex and a base:* in one with "disability not diagnosed."

Persistent râles were heard in the two cases of malignant tumor, one of bronchitis and one "post-influenza." The two cases of malignant tumor also showed parenchymatous changes in the X-ray atypical of tuberculosis. Atypical X-ray changes were also seen in the cases of pulmonary abscess, mitral regurgitation and in one of the "disability not diagnosed."

The patient with rheumatism and purpura died within a year of endocarditis, the one with gall stones died of influenza within a year. One patient with malignant tumor died of carcinoma of the lung within a year, the other died of Hodgkin's disease within three years. One "disability not diagnosed" case died of endocarditis after five years. Twenty had left the Sanatorium for less than a year. All others have remained well from one to seven years with the following exceptions: one syphilis case had hemoptysis and elevation of temperature after two years, and two cases with "disability not diagnosed" had hemoptysis without other symptoms after one and three years, respectively, and are now well.

The subcutaneous tuberculin test was given to 159 patients. Sixty-four failed to react either constitutionally or focally to a repeated dose of 10 mgm. O. T., while one reacted constitutionally but not focally to 10 mgm. O. T. All others reacted constitutionally to various other smaller doses. Focal reactions were noted by physical signs only as follows: the one case each of sinus disease, periapical infection of teeth and post-poliomyelitis paralysis, one case of post-influenza, two of nervous disorders, two "disability not diagnosed." In all these instances fine râles were noted and the likelihood of error was borne in mind.

None of the 203 cases has developed demonstrable pulmonary tuberculosis unless the occurrence of hemoptysis in the three patients (1.5 per cent) may be regarded as such without further evidence. It must be borne in mind that all of these patients had been sent to the Trudeau Sanatorium with a positive diagnosis of pulmonary tuberculosis.

2. THE SUSPECTED GROUP

In this group of 61 cases were included one case each of aspergillosis, suspected malignant tumor of the lung, tuberculous rib, colitis, post-pneumonic disability, suspected bronchiectasis, bronchitis with thyroid disturbances, spontaneous pneumothorax and mitral regurgitation;

2 cases each with thyroid disturbance, suspected syphilis, cervical adenitis and bronchitis; 10 cases with nervous disorders and 34 cases in which disability was not diagnosed.

Temporary râles occurred as follows: *1. Moderately coarse at an apex:* in one patient whose disability was not diagnosed. *2. Moderately coarse at a base:* in one case of bronchitis and two with "disability not diagnosed." *3. Moderately coarse at an apex and a base:* in one case of bronchitis with thyroid disturbance. *4. Moderately coarse in the centre of a lung:* in one case of mitral regurgitation. *5. Fine at an apex:* in 4 cases with "disability not diagnosed." *6. Fine at a base:* in one case with "disability not diagnosed." *7. Fine at an apex and a base:* in one case with "disability not diagnosed."

Persistent râles were found as follows: in one case of bronchiectasis with fine râles at a base, in one of bronchitis with moderately coarse râles at an apex and a base, in two of bronchitis with moderately coarse râles at a base, in one with "disability not diagnosed" with fine râles at the apex and in one with moderately coarse râles at an apex, and in one with fine râles at an apex and moderately coarse râles at the base.

Parenchymatous X-ray changes, slight in intensity and extent and atypical of tuberculosis, were noted in the following cases: one of aspergillosis, one of suspected malignant tumor, one with thyroid disturbances, two of bronchitis, one of cervical adenitis (X-ray changes at the base), one of neurasthenia and 5 with "disability not diagnosed."

Eleven cases gave a history of positive sputum, 3 of a previous wet pleurisy and 16 of a previous hemoptysis.

The subcutaneous test was given to forty-four. Fifteen failed to react to a repeated dose of 10 mgm. O. T. Twenty-nine reacted constitutionally and 13 focally as determined by physical signs. None reacted focally as seen in the X-ray plate.

Nine were discharged less than one year ago. The patient with probable malignant tumor of the lung died within a year of bronchopneumonia. All others remained well from one to seven years except as follows: The patient with a tuberculous rib developed wet pleurisy within a year, and hemoptysis and fever within two years. He has had a demonstrable pulmonary tuberculosis with positive sputum but is now arrested. One case of cervical adenitis with basal parenchymatous changes developed an apical parenchymatous X-ray change within two years and has now a definite quiescent pulmonary tuberculosis.

3. THE NONCLINICAL GROUP

Eleven cases were classified as nonclinically tuberculous. One had bronchitis due to some form of sensitization, one an antrum infection following influenza and 9 had no other diagnosed disability. The 2 first-mentioned cases had temporary moderately coarse râles at the base and slight parenchymatous changes at the apex. One of the "disability not diagnosed" cases had temporary moderately coarse râles at the apex. Seven "disability not diagnosed" cases had slight parenchymatous changes at the apex and two had them in the central portion of the lung. All eleven were given the subcutaneous test. Three failed to react to a repeated dose of 10 mgm. of O. T. All others reacted to various smaller doses constitutionally, but not focally as determined by physical signs or X-ray. Seven have been discharged less than a year; the others have remained well from two to three years and have developed no active tuberculosis.

DISCUSSION AND SUMMARY

Of 203 nontuberculous cases admitted to Trudeau Sanatorium, 126 had no recognizable clinical disability. Of the 77 who were found to have a definite reason for disability, some form of nervous disturbance was found to be the most frequent cause (21 instances). Disability in these instances was manifested principally by languor, loss of weight, anorexia, etc. Next in order of frequency were the post-influenzal debilities (13 cases). For the most part these had the usual temporary symptoms of bronchitis accompanied by languor, etc. A few had a more lasting bronchitis. Bronchitis of unknown origin occurred twelve times. Thyroid disturbances occurred in 5, syphilis in 4, enteroptosis in 4, malignant tumor of the lung in 2 and in one instance each the following conditions were found,—frontal sinus infection, periapical infection of all teeth, tonsillitis, tuberculous tonsils (removed previously), pulmonary abscess, bronchiectasis, endocarditis, mitral regurgitation, rheumatism with purpura, Raynaud's disease or arthritis, arthritis deformans with psoriasis, nephritis, renal calculus, gall stones, post-poliomyelitis paralysis, ovarian cyst.

In 126 cases no definite disability was diagnosed. A large proportion had "colds" or were run down from lack of physical rest. Recuperation followed closely upon taking such rest.

From the above it would seem that too much importance is placed upon the toxic symptomatology in diagnosing tuberculosis rather than upon the activity of the disease when its presence is assured by other methods. Furthermore, too great an importance is placed upon the clinical findings at one examination. It frequently takes time to diagnose pulmonary tuberculosis. It cannot always be done at one examination, and repeated observation and examinations are often necessary.

From a survey of the "suspected" group it can also be said that a diagnosis cannot always be made definitely, with justice to the patient, even after prolonged examination. Other conditions may be present at the same time as the pulmonary tuberculosis or they may closely simulate it. It is most difficult at times to draw the dividing line between presence and absence of this disease; the patient should be protected physically as well as socially. The easiest thing to do from the standpoint of the physician is to say that tuberculosis is present.

It is gratifying to know that only 2 of 264 suspected or negative cases developed definite pulmonary tuberculosis (0.75 per cent), but both of these were known, however, to be tuberculous. All 3 definite or questionable cases of malignant tumor of the lung are dead, the causes of death having been carcinoma of the lung, Hodgkin's disease and bronchopneumonia. Four patients with definite and 2 with probable syphilis are living and well from four to seven years after discharge. Three with definite syphilis failed to react to a repeated subcutaneous dose of 10 mgm. O. T. The other three had no subcutaneous tuberculin test.

THE SUBCUTANEOUS TUBERCULIN TEST

This test was given to 214 patients: 82 failed to react to a repeated dose of 10 mgm. O. T.; 132 reacted constitutionally and of these, 21 reacted focally as determined by physical signs. Forty per cent of the nontuberculous, 34 per cent of the "suspected" and 27 per cent of the "nonclinical" failed to react. Temporary fine râles were found immediately after the constitutional reactions in 12.5 per cent of the nontuberculous, 29.5 per cent of the "suspected" and none of the "nonclinical" cases.

CONCLUSIONS

1. It must always be borne in mind that definite clinical pulmonary tuberculosis may develop at any time in a certain number of subliminal cases.

2. It is unwise to accept from one year to another a negative diagnosis of clinical pulmonary tuberculosis although in these cases the percentage is so small as to be almost negligable.

3. A patient who fails to react to a repeated dose of 10 mgm. of old tuberculin rarely, if ever, develops active clinical pulmonary tuberculosis.

4. When all of the five suggested diagnostic criteria are absent a negative diagnosis of clinical pulmonary tuberculosis can be safely made.

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AN ATTEMPT TO CLASSIFY BY MEANS OF THE X-RAY CASES OF SUSPECTED AND DEFINITE PULMONARY TUBERCULOSIS SHOWING LESS THAN A DEFINITE PARENCHYMATOUS X-RAY LESION[1]

A Preliminary Report

FRED H. HEISE AND HOMER L. SAMPSON

Almost every diagnostician encounters, at times, cases in which no more definite evidence of pulmonary tuberculosis presents itself than the history of an hemoptysis or of tubercle bacilli having been found in the sputum or of a previous wet pleurisy in which no definite lesion can be seen in the X-ray plate. It was hoped that in this type of case something could be gained by a more critical study of the X-ray plates and be of aid in diagnosis. Accordingly, a small number of cases were selected from each of the following groups: (1) nontuberculous, (2) those with a history of hemoptysis, (3) those with a history of pleurisy with effusion, (4) those whose sputum was reported as previously positive and (5) those presenting a combination of two or more of the findings under (*2*) (*3*) and (*4*). The X-ray films of these patients were then freely mixed and an attempt was made to place each film in a group representing the closest definite X-ray evidence of pulmonary tuberculosis. The manner of classification was as follows: Those films showing nothing but increased density or enlargement of the root shadows were put in *group 1*, or the *root* group. *Group 2* comprised those showing a few or fairly numerous isolated tubercles. Films showing definite beading along the trunks were placed in *group 3*. In *group 4* were those showing definite pleuritic changes and in *group 5* were placed those films which showed indefinite but probable parenchymatous changes.

When thus classified, it was found that the number of films in each group were as follows: *group 1*, 32, *group 2*, 22, *group 3*, 57, *group 4*, 14 and *group 5*, 45.

The incidence of a history of hemoptysis or of pleurisy with effusion, or of tubercle bacilli in the sputum and râles, was next ascertained for

[1] From the Trudeau Sanatorium, Trudeau, New York.

each group. Table 1 shows the incidence of these in each group, as well as in an unselected group of 412 nonparenchymatous cases.

From the table it is seen that hemoptysis occurred most frequently in the *probable parenchymatous* and *isolated tubercles* groups. Pleurisy with effusion was naturally highest in the *pleurisy* group and next frequent in the *probable parenchymatous* and *isolated tubercles* groups. Tubercle bacilli were found at the sanatorium in all groups except the *isolated tubercles*, but most frequently in the *probable parenchymatous* group. Moderately coarse râles were found at an apex most frequently in the *pleurisy* group and at the base in the *probable parenchymatous* group. The striking feature, however, is the absence of a history of

TABLE 1

	NUMBER	HEMOPTYSIS		PLEURISY WITH EFFUSION		BACILLI				RALES						NO PLEURISY, HEMOPTYSIS, BACILLI OR RALES		DEAD	
						Previous		Residence		Moderately Coarse				Fine					
										Apex		Base		Apex or Base					
		Number	per cent	Number	per cent	Number	per cent	Number	per cent	Number	per cent	Number	per cent	Number	per cent	Number	per cent	Number	per cent
Group 1: Root	32	4	13	2	6	5	16	1	3	1	3	2	6	5	16	14	43	2	6
Group 2: Isolated tubercles	22	5	22.5	3	13	2	9	0		1	5	2	9	8	37	7	32	0	
Group 3: Peritruncal tubercles	57	12	21	5	9	13	23	5	9	3	5	3	5	7	12	18	32	2	3.5
Group 4: Pleuritic	14	2	14	5	36	1	7	1	7	2	14	0		2	14	2	14	1	7
Group 5: Probable parenchymatous	45	13	28	7	16	7	16	6	14	4	9	10	22	6	14	8	17	5	11
Mixed group of nonparenchymatous cases	412		12		4		8		4		2		8		7		58		2

pleurisy with effusion or of hemoptysis and the absence of tubercle bacilli and râles in the *root*, *isolated tubercles* and *peritruncal* groups. In other words, the more nearly the X-ray findings approach the parenchymatous type, the more frequently one or more of the criteria of a positive diagnosis are found.

There were two deaths in the *root* group, one caused by diabetes mellitus and the other by general paralysis. The reports covered four years or more in all but four of the living patients. There have been no deaths in the *isolated tubercles* group. All of these but four had reports for four years or more. One death from embolus and one from septic peritonitis occurred in the *peritruncal* group. Four-years or more reports were received from 84 per cent of the living in this group.

In the *pleurisy* group one death occurred, after five years, from tuberculous peritonitis following removal of a "tumor." All but one patien sent in reports for four years or more. In the *probable parenchymatous* group five deaths occurred as follows: two from influenza, one from accident, one from pulmonary tuberculosis and one from sarcoma. The last also had an inactive pulmonary tuberculosis. All but two of the living gave four or more years' reports.

Therefore, it can be said that no deaths from pulmonary tuberculosis occurred in any of the groups with the exception of 2 per cent of the *probable parenchymatous*. One patient of the *pleurisy* group died of tuberculous peritonitis after five years. Nearly all of the patients in all groups rendered reports for four years or more.

In a nonselected group of 412 patients, in whom no definite parenchymatous tuberculous lesion could be found, 98 per cent were alive after four years and 2 per cent dead. Deducting from the 170 cases considered those having no suggestive or positive findings (49), we have 121 patients who had a pleurisy with effusion or an hemoptysis or râles or a history of positive sputum and in whose X-ray films no unquestioned parenchymatous changes, characteristic of pulmonary tuberculosis, could be seen. Of these only two have died within four years of tuberculosis (1.7 per cent): one of pulmonary and one of peritoneal tuberculosis.

CONCLUSIONS

1. The number of cases in each group considered is far too small to draw any definite conclusions. Nevertheless, it is noteworthy that no deaths occurred from pulmonary tuberculosis except in the probable parenchymatous group. The patient dying of tuberculous peritonitis, in all probability, had a pulmonary tuberculosis at the time of the pleurisy with effusion.

2. Although a patient may have had an hemoptysis or a pleuritic effusion or a history of positive sputum or râles and the X-ray not show a characteristic tuberculous parenchymatous lesion, the prognosis seems to be quite good, since only 1.7 per cent of 121 such cases have died of tuberculosis within four years.

TUBERCULOSIS OF THE PANCREAS

With Report of a Case[1, 2]

S. L. VANVALZAH[3]

In over 200 autopsies on tuberculous subjects at the Fitzsimons General Hospital, Denver, definite tubercles have been found in the pancreas but once. Search of text books on both medicine and pathology revealed only passing references to the condition, merely mentioning that it did occur. Nothing definite on the subject was found except that it is a rare condition.

In reviewing the available literature some very interesting articles were found in both French and German, with several references to Russian and Polish articles. But two or three references were in English, and two of these were case reports, one of which was of a cystic pancreas. In the French literature, the Mayos were mentioned once, but no bibliographical reference was made, and no reference to their work was found in any indices.

The most comprehensive article on the subject was a *Thesis* written by Loheac (1) in 1899. Several more recent articles were reviewed, but none of them added anything more than confirmation of the material quoted by him. Apparently, the first reference to the subject was a memoir by Harles (2), written in the middle of the eighteenth century on pancreatic phthisis and the cachexia accompanying cirrhosis and abscess of the gland. Other references were made by Varnier (3) in 1755, Glotigny (4) in 1757, and in 1836 Mondier (5) added more in a work on diseases of the pancreas. Aran (6) in 1846 published a report of a case of abscess of the pancreas with abnormal pigmentation of the skin. Several others were reported subsequently, up to 1899, when Loheac's *Thesis* was published in Paris.

Here it must be recalled that the early observers were not absolute in diagnosis, for it was not until the middle of the nineteenth century that there was definite concurrence of opinion on the histological structure

[1] From the laboratory service, Fitzsimons General Hospital, Denver, Colorado.

[2] Published with the authority of the Surgeon-General.

[3] Major, Medical Corps, United States Army.

of tuberculous lesions. Although Laennec described tuberculosis much earlier his work was disputed for many years, and it was much later when Koch demonstrated the tubercle bacillus.

Carnot (7), in 1897–1898, published his experiments on the different forms of pancreatitis. Several authors have since reported on the same work, and have only corroborated his findings. It is true that some additions to the study have been made, but they are of minor consequence. Carnot showed the extreme difficulty of reproducing clear-cut tuberculous lesions in the pancreas. The fact of greatest interest in all these experiments is that, no matter what the source of inoculation, true tubercles almost never occur in the pancreas unless there has been severe disturbance of the blood supply of the gland or some occlusion of the ducts.

Carnot states,

> With a virulent tubercle bacillus, the gland passes the first weeks reacting against it. The tissues are not yet organized. At the end of a week one still sees the bacilli in the gland. Sections are filled with leucocytes and the bacilli are weakened in virulence. Inoculating a guinea pig with this material gives it only a localized tubercle, the chancre of inoculation, with no extension at the end of a month and a half. If one will wait, the virulence diminishes still more and the bacilli disappear, so that not a single one can be found in the tissue on section, while the connective tissue becomes organized where it was filled with leucocytes. With less virulent bacilli one gets a pericanalicular, perivascular and even a pericellular sclerosis. Tuberculin will produce this same reaction.

On this sclerosis of the pancreas in tuberculosis, all authorities agree, but most hesitate calling it a truly tuberculous reaction, as it may result from many toxic infections other than tuberculosis. Tubercles seen in the gland parenchyma are rare indeed, and from the above experiments and those of Klippel and Chabrol (8) and, later, Mayer (9) it is apparent that the pancreas has a most potent protective agent against the tubercle bacillus.

There is, however, a true histological tubercle produced at times, followed by necrosis and caseation due to the action of the bacillus. Here we find two types of lesions, the miliary, scattered lesions appearing grossly as small yellow or grayish dots and microscopically as more or less caseated nodules surrounded by degenerated parenchyma cells. This type is probably due to hematogenous dissemination and represents the reaction of the pancreas to a generalized miliary tuberculosis.

The other type is the cavernous. This, by some, is considered to be due to spread by way of the pancreatic ducts, and is much more rare. Cavities are few in number, and often single and of variable size. The walls are rough and irregular, and may be covered with small tubercles. The contents represent the debris of the broken-down tissue. These cavities have always been found very close to or associated with the excretory ducts, and usually communicate directly with them. They are most apt to be anterior in location, and may be covered by an adhesive peritonitis, fastening the pancreas to the overlying stomach.

There is still disagreement among authors as to the lymphatic supply of the pancreas. There are always lymphatic nodes in the vicinity of the organ. In tuberculosis these are frequently enlarged and may be caseous. By some authorities it is claimed that lymph channels, and even small accumulations of lymphatic tissue or even nodes, exist among the parenchymal cells of the pancreas.

Cases of extensive lymphatic tuberculosis about the pancreas are not rare, and even large nodules well imbedded in the pancreatic tissue, compressing the gland structures and apparently part of the gland, are frequently seen. Some of these may quite likely be called pancreatic tuberculosis on first sight and if, as above stated, the lymphatics do extend into the gland parenchyma, such lymphatic extension is easily possible. The sclerotic reaction is always present in these types of tuberculosis.

The disease has usually been found associated with pulmonary or enteric tuberculosis. Walter-Salis (10) quotes 6 cases of primary tuberculosis of the pancreas, but they are indefinite. In our series of autopsies the intestine has almost always been found ulcerated in cases of pulmonary tuberculosis, although few of these cases have manifested clinical signs or symptoms of any intestinal disturbance which would lead one to suspect intestinal tuberculosis.

In the pancreas there are at least two great routes of infection open, the blood stream and extension along the excretory ducts, with the probability of the lymph channels as well. Mayer's experiments seem to prove that interference in the flow of the pancreatic juice makes possible infections which might not otherwise take place. His experiments were made by tying off, but we can see no great difference in occlusion by pressure from enlarged caseous lymph nodes or even in severe sclerosis of the organ.

Kudrewetzki reports 15 cases in 128 autopsies: 6 miliary, 7 chronic tuberculosis, and 2 tuberculosis in the vicinity. This is far more than in our experience, and more than any other series reported. Mayer had 10 cases in 184 autopsies. In 8 of these there was involvement of surrounding lymphatics. Four were in children. Two of the cases were in generalized miliary tuberculosis, which formed 42 cases of the series, 3 were in 20 cases of partial miliary and 5 were in 122 cases of chronic tuberculosis.

Lesions may be invisible on gross examination, but show as typical tubercles under the microscope, with giant cells and tubercle bacilli. The mere presence of tubercle bacilli in a gland not showing other histological changes does not mean disease, as these may be rendered innocuous by the secretions.

We found no other detailed symptomatology than that given by Loheac. The symptoms are only manifest late in the disease, when all of them are practically those of pancreatic insufficiency; namely, disturbances of digestion and assimilation, disturbances of glucose metabolism and symptoms of pressure on the solar plexus, pain and melanodermia. A sensation of weight in the epigastrium and pain are quite constant and meteorism is habitual. Diarrhea may or may not be present, and if present may be due to enteritis. Glycosuria may be present, but is not constant. A case is quoted which excreted 69 grams of sugar per litre. Emaciation developes rapidly, and becomes extreme.

Pain is significant, and may dominate the scene. "Intermittent, dull and vague at the beginning, it soon becomes continuous and permanent with acute paroxysms, which may draw cries from the patient. The cause is pressure on the solar plexus, either by localized peritonitis or by the enlarged lymphatics surrounding. The patient may assume a characteristic attitude in bed, lying on the left side, with spine and legs flexed, and not caring to move. Ingestion of food may augment the pain."

Pigmentation of the skin comparable to that seen in Addison's disease is frequent, but it is more often only a brownish pigmentation. Loheac also states that this is a result of pressure on the solar plexus.

Sclerosis of the gland may give rise to insufficiency, but this is rarely so marked as to be brought to the attention of the physician.

The disease is chronic and coexistent with other tuberculous manifestations, and rarely or never is the cause of death, though it probably hastens the end.

Diagnosis of the disease is difficult. It is rarely primary or isolated, and the signs of insufficiency do not develop until there has been extensive destruction. However, certain signs and symptoms developing in a case of pulmonary tuberculosis should lead one to suspect involvement of the pancreas. The most important signs are pain, rapid and excessive emaciation and melanodermia.

The treatment is the same as for any other type of tuberculosis. Even if diagnosed, extirpation of the pancreas would be out of the question.

Here we shall give one case quoted by Loheac from Sendler:

A woman aged 54, attacked 9 months ago by gastric trouble, with extreme loss of weight. On examination, at the level of the epigastrium is a hard, nodular tumor. No trouble with stomach function. Diagnosed malignant neoplasm of the pancreas. At operation it was found that the head of the pancreas was the site of a tumor as large as a walnut. The pancreas, as well as a few swollen lymph nodes behind the stomach, were removed. The patient left the service after 2 months completely cured. Histological examination of the tumor made by Dr. Thoma showed that it was a tuberculous lymphoma of the head of the pancreas. We ought to add that the patient did not present any other manifestations of tuberculosis.

The report of our case follows:

J. S., Porto Rican, age 22. Family history negative. *Personal history:* Denies venereal disease; contracted malaria in Porto Rico, June, 1922; usual quinine treatment, but did not fully recover. Began losing weight, followed in a few weeks by night sweats and nose-bleed. Cervical lymphatics swelled and became painful. Diagnosed pulmonary tuberculosis and sent to Fort Totten, New York, in November, 1922; thence to Fitzsimons, Colorado, arriving December 4, 1922. Very weak and emaciated. *Diagnosis:* Tuberculosis, pulmonary, chronic, active all lobes both lungs. Lesions conglomerate, nodose and mixed. Ankylostomiasis. Nephritis. Observation for tuberculous peritonitis.

Temperature ranged between 101° P.M. and 103° P.M. Appetite poor. Expectoration slight. He was the uncomplaining type of patient, possibly due to poor command of English, but occasionally complained of pain in the abdomen, especially on the right side opposite the umbilicus, and about 2 inches below the costal margin. Examination at these times showed some tenderness, and a board-like rigidity to the right of the rectus muscle. A great portion of these symptoms would disappear following free evacuation of the bowels. Stools were loose and watery and at times involuntary.

Symptoms and asthenia grew progressively worse. Sputum positive for tubercle bacilli. Urine showed albumen and casts, but no sugar. Stools showed hookworm ova. Wassermann negative. Died January 5, 1923.

AUTOPSY

An extremely emaciated male, of quite dark complexion which may be due to his nativity. Pericardial sac contained 350 cc. of clear straw-colored fluid. No other signs of pericarditis. Lungs full of caseous nodose tubercles about the size of a pea. No cavitation. Lymph nodes of neck and thorax all

FIG. 1. GROSS SECTION OF PANCREAS AND SURROUNDING LYMPH NODES

Note tubercles in the pancreas

enlarged and succulent; no caseation. Plastic peritonitis. Mesentery full of enlarged caseous lymph nodes, varying in size from a pea to a fair-sized egg. Few small ragged ulcers in the intestine. Lesser peritoneal cavity contained about 400 cc. of clear straw-colored fluid. Liver showed advanced chronic passive congestion, but no macroscopic tubercles. Spleen enlarged about three times, and full of caseous tubercles about the size of a filbert. The pancreas was almost completely surrounded by a mass of caseous lymph nodes, some of which appear to have enlarged within the septa of the gland, in certain areas almost completely isolating islands of the parenchyma. The

Fig. 2

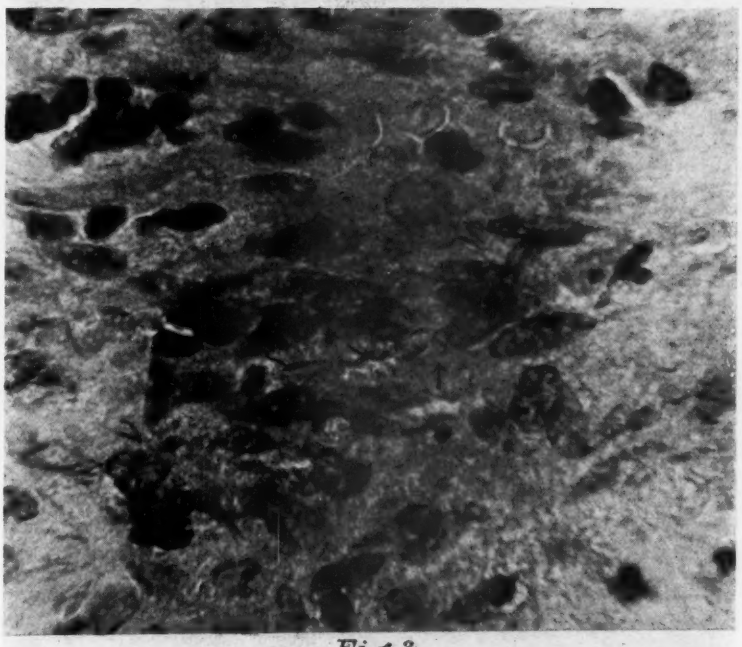

Fig. 3

FIG. 2. LOW-POWER MAGNIFICATION OF TUBERCLE

The circle marks location of figure 3

FIG. 3. OIL-IMMERSION MAGNIFICATION, SHOWING STAINED TUBERCLE BACILLI IN TISSUE OF PANCREAS

organ was not more than half its normal size. On section small opaque grayish dots could be seen in the gland substance. These were considered true tuberculous foci in the parenchyma. The kidneys showed a diffuse nephritis, with scattered tubercles.

Histological examination of the pancreas showed a diffuse sclerosis, with degenerative changes in the cells of the islands of Langerhans and numerous small necrosed areas in the gland tissue, with larger caseated areas. In and about these areas, tubercle bacilli were easily demonstrated by either Ziehl-Neelsen or MacCallum's method. Neither endothelioid cells nor giant cell formation were seen in any areas. The gland cells undergo degeneration and caseation follows, without typical tubercle formation as usually seen in other organs. These areas show up as distinct caseated areas in the substance, with no apparent relationship with the involved lymphatics.

In this case, then, we have a young man with generalized tuberculosis with the following symptoms: Rapid and extreme emaciation, severe pain in the lower epigastric region, which is so severe at times that it caused him to complain, diarrhea at all times though it is noted that evacuation caused the pain to subside, and marked pigmentation of the skin although this may be and probably is in part due to the nativity of the subject. These, in a case of tuberculosis, should suggest some unusual complication. The absence of glycosuria is not remarkable in itself, but from the degeneration of the Langerhans cells is not what one would expect.

CONCLUSIONS

1. Tuberculosis of the pancreas, when we consider it to mean the formation of tubercles in the gland substance, is a rare disease.
2. Tuberculous or rather toxic sclerosis of the gland is frequent, but is not diagnostic of tuberculosis.
3. Infection has two, and quite probably three portals of entrance, the blood, the ducts and the lymphatics.
4. There is an apparent inherent quality of the pancreas which renders it relatively free from infection. This is either the pancreatic juice or some substance elaborated by the cells.
5. The disease produces a fairly definite chain of symptoms which may be diagnostic but which may appear too late to prove of any but diagnostic interest.
6. There is no apparent cure.

7. An interesting point is the relative freedom of the pancreas from tuberculous infection, and the possibility of the gland aiding in overcoming tuberculosis in other parts of the body.

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FATAL SPONTANEOUS HEMORRHAGE INTO THE SPLEEN FROM A TUBERCULOUS ULCER OF THE BOWEL

Report of a Case[1]

S. A. LEVINSON

Enlargement of the spleen may usually be observed in many acute infectious diseases, such as typhoid fever and malaria. Certain diseases of the hematopoietic system, the leukemias, jaundice resulting from alcoholism, Banti's disease, and Gaucher's splenomegaly, among others, may be associated with varying degrees of splenic enlargement. Other conditions, like cirrhosis of the liver, chronic passive congestion of the spleen, and obstruction of the splenic vein by abscess, tumor or infarcts, as well as inherited syphilis or rickets, may at times show evidences of chronic splenic tumor. Kaufmann (1) mentions aneurysm of the splenic artery and, occasionally, amyloidosis of the spleen as additional causes. Spontaneous rupture of the spleen, aside from mechanical injuries, may occur in the following conditions: typhus abdominalis, miliary tuberculosis, leukemia, pseudoleukemia and recurrent fever. Kaufmann mentions a case in which aneurysm of the splenic artery resulted in a secondary enlargement of the spleen with rupture of the latter into the abdomen. It is because of the rarity of the occurrence of hemorrhage of the spleen that the following brief clinical and pathological condition is here reported.

Patient L. Mc., age 18 years, colored, was admitted to the Municipal Tuberculosis Sanitarium, May 31, 1923. Family history negative. He was operated upon 8 years ago for "enlarged glands of the neck." The present illness started 2 years ago with loss of weight (about 16 pounds), slight cough and occasional night sweats. Physical examination at the time the patient was admitted to the hospital showed marked emaciation of chest, arms, and leg muscles; marked dulness in left upper quadrant of abdomen, and enlarged, palpable inguinal lymph nodes. Physical examination of chest showed emphysema in right lung and upper lobe of left, and pleurisy with effusion in left

[1] From the laboratory of the Municipal Tuberculosis Sanitarium, Chicago, and the Department of Pathology, University of Illinois College of Medicine, Chicago.

lower base. The heart was pushed over toward the right. On subsequent examination the spleen was found to be enlarged and easily palpable. Roentgen-ray examination of chest was made June 1, 1923. This showed a heavy, mottled infiltration throughout the chest. Base of left lung was dense. No tubercle bacilli were found on repeated examinations of sputum. Blood Wassermann was negative, and tuberculosis complement fixation test 2 plus. Urine negative. Erythrocytes 3,780,000; leucocytes 11,000; hemoglobin 60 per cent. Differential blood count: polymorphonuclear neutrophiles, 85 per cent; eosinophiles, 2 per cent; transitionals, 3 per cent; small lymphocytes, 6 per cent; large lymphocytes, 4 per cent.

The temperature as a rule was normal, the highest being 99.5°F. The pulse rate varied from 80 to 100. Three days before patient died large quantities of blood clots were expelled from the rectum. *Clinical diagnosis* on admission, May 31, 1923, was Hodgkin's disease and glandular tuberculosis.

The patient died August 7, 1923.

The *necropsy*, which was performed the following day, revealed the following pathological findings: calcified tuberculous lesion in left apex; caseous tuberculosis in tracheobronchial, axillary, mesenteric and retroperitoneal lymph nodes; tuberculous ulceration of small intestine, caecum, ascending, transverse, and descending colon; tuberculous perforation into splenic portion of colon; tumor of spleen with miliary tubercles and marked hemorrhages and blood clots in spleen and descending colon (the abdominal cavity did not contain any blood clots); miliary tuberculosis in both lungs; bullous emphysema in both lungs; cloudy swelling of heart muscle; dilatation of right ventricle and auricle with slight hypertrophy of right and left ventricles; chronic parenchymatous nephritis; fatty degeneration and slight fibrosis of liver.

Examination of the spleen showed that this organ was greatly enlarged, the spleen and most of the blood clots contained within it weighing 1420 gm. This organ was found to occupy almost the entire area in the left side of the abdominal cavity. It was soft and friable, adherent to the stomach and splenic portion of colon, and was difficult to remove in one mass. The entire colon was cut open, and in the region of the splenic flexure of the colon a perforated ulcer was seen extending into the spleen. On account of the friability of the latter a detailed examination of the splenic vessels could not be made for aneurysm or thrombosis. Upon removing the spleen the capsule along the greater curvature was found markedly thickened (about 0.5 cm. in thickness). The spleen was reddish in appearance and cut very easily, and on the cut surface numerous miliary tubercles could be observed. In its central portion there was an extensive deposit of blood clots arranged in a lamellated formation.

Microscopic examination of the spleen showed an extensive deposit of miliary tubercles, with giant cells and caseation. Throughout the section numerous hemorrhagic areas could be seen.

The descending colon was filled with a large blood clot. The mucosa of the colon was smooth and glistening, and covered with numerous tuberculous

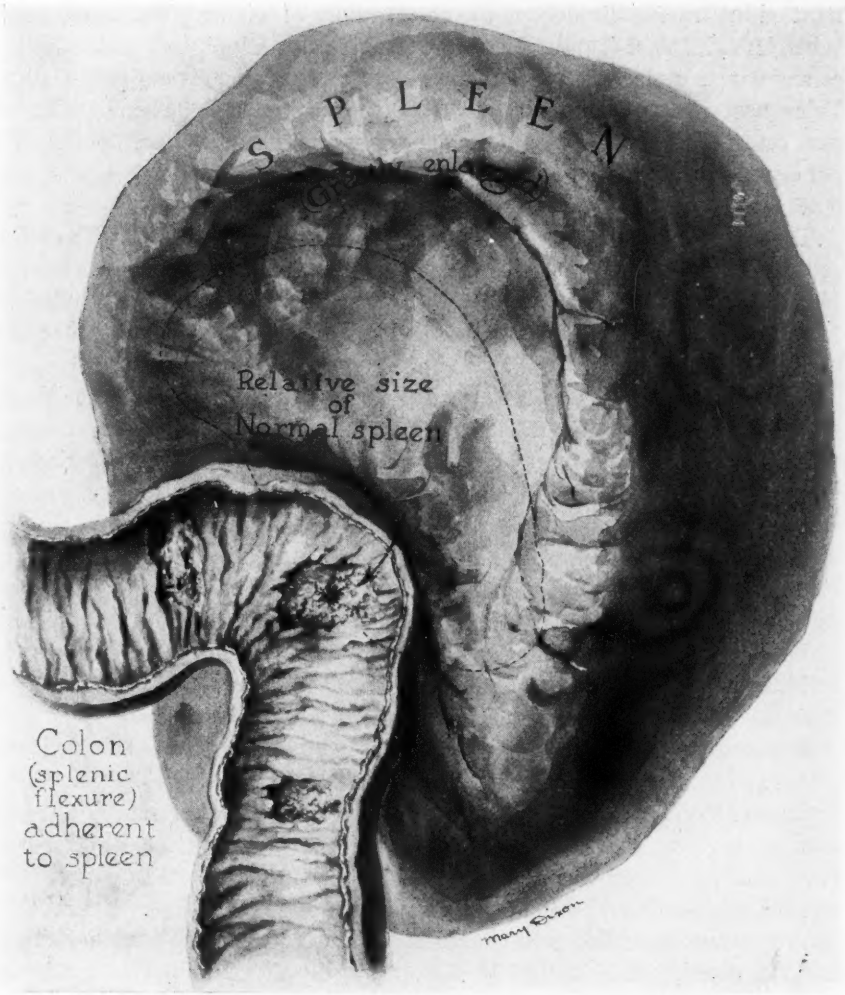

FIG. 1

The arrow points to the tuberculous lieno-colic fistula. Nonperforating ulcers are seen in transverse and descending colon.

ulcerations. [One, previously described, had perforated into the spleen (figure 1).

The cause of death was hemorrhage from the spleen into the descending colon. The associated factors were miliary tuberculosis of lungs and spleen with a generalized caseous tuberculosis of tracheobronchial, mesenteric, retroperitoneal and axillary lymph nodes, and a tuberculous ulceration of the small and large intestine.

COMMENT

This case is reported to emphasize the relative infrequency of extrapulmonary conditions which suddenly prove fatal to the patient. Enlargement of the spleen and miliary tuberculosis are not uncommon conditions in pulmonary tuberculosis. Likewise, intestinal tuberculosis is a rather common occurrence in far advanced pulmonary tuberculosis and the autopsy records of the Municipal Tuberculosis Sanitarium show 85 to 90 per cent of intestinal involvement. Nevertheless, perforation of one of these tuberculous lesions of the bowel would usually be to the free abdominal cavity. In the condition here reported perforation of the tuberculous intestinal ulcer had occurred into the spleen. Recently Moench (2) reported an erosion of the splenic artery and a fatal hemorrhage in acute pancreatitis.

According to Litten (3), the spleen is enlarged in about 70 per cent of the cases in pulmonary tuberculosis. Hershfeld (4) states that in the majority of cases of tuberculosis the spleen becomes enlarged, but the enlargement is only relative, and it is only in the unusual conditions of pulmonary or extrapulmonary tuberculosis that the spleen becomes recognizable clinically.

The history of the patient is also unusual in that there were no typical symptoms associated with hemorrhage from the spleen until three days before he died. The enlarged lymph nodes removed from the neck about 8 years ago undoubtedly were tuberculous. The Widal examination and blood culture for typhoid fever, as well as stool examination for typhoid bacilli, were negative. Repeated blood examinations and clinical findings also proved negative for malaria.

In considering the necropsy findings, especially the pathology of the splenic flexure of the colon and the spleen itself, one must consider at least two possible factors responsible for the hemorrhage. Erosion or aneurysm of the splenic vessels would produce hemorrhage into the abdominal cavity, as well as into the spleen, and death of the patient would occur sooner than it did. It is possible, however, that the tuberculous ulceration in the splenic flexure of the colon perforating into the

spleen (making a fistulous opening from the bowel into the spleen) caused a destruction of the splenic tissue and an erosion of the splenic vessels within the spleen. As a result of the continuous breaking down of splenic tissue and hemorrhagic deposits, the spleen became secondarily enlarged, and at the same time a defensive mechanism was set up by nature in the form of a thickened capsule around the spleen. Hemorrhage into the spleen may have continued relatively slowly, the newly formed clots being deposited around the old organized and lamellated clots. This continued until oozing of the blood, and eventually a large hemorrhage, occurred, not only into the spleen, but forced its way through the fistulous opening into the colon. The descending colon became filled with blood and the patient passed large blood clots. This condition continued for several days until the patient died.

SUMMARY

A case of spontaneous fatal hemorrhage from the spleen into the bowel, with a tuberculous lienocolic fistula, is reported.

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PERFORATION OF THE ILEUM DUE TO A TUBERCULOUS ULCER

Report of a Case[1, 2]

W. B. JAMESON

When the writer found, at autopsy, an acute peritonitis due to a perforation of the ileum over a tuberculous ulcer, Dr. Henry A. Gorman commented on its rarity. It was the first case of the kind I had seen. I had never before heard of one nor seen mention of any in a medical journal. The available library was consulted. Pepper's *System* did not mention it and Ziegler's *Pathology* (not a late edition) did not describe it. Two able books on tuberculosis, *Klebs* and *Fishberg*, do not mention the condition and Osler's *Modern Medicine* does not enumerate it among the complications. In *Monographic Medicine* Elsner states that in children there is rarely intestinal perforation and there is no tendency toward spontaneous repair. Under these circumstances to give an account of one case does not appear to be needlessly adding to tuberculosis literature.

Patient A. F. N., age 49, had diphtheria in 1904, but made good recovery and remained well until an attack of typhoid fever in 1917. He was in bed 4 or 5 weeks and 3 or 4 weeks later returned to his work as machinist. His recovery was not good; his weight, strength and endurance did not become normal and later, in 1917, he spat blood.

In November, 1918, he was admitted to Mont Alto State Sanatorium with tuberculosis of the right upper lobe, and middle lobe and apex of the upper lobe of left lung, and was classed as far advanced. He was able to live in the camp, but the tuberculous process extended to the right lower lobe and gradually he failed, so that he could not travel to the dining room through the winter storms, and he was sent to Hamburg on March 29, 1922. His condition justified his going to the dining room near his ward and doing light exercise. The right lung was entirely tuberculous and the process was moder-

[1] From the State Sanatorium for Tuberculosis, Hamburg, Pa.

[2] This report has the approval of Dr. Henry A. Gorman, Medical Director, State Sanatorium for Tuberculosis, Hamburg, Pa., and of Dr. Charles H. Miner, Secretary of Health of Pennsylvania, Harrisburg, Pa.

ate in the left upper lobe. Cavitation was extensive in the right upper lobe. He failed steadily, the right lung became the seat of numerous cavities, and for many months before death he was a bed patient and at the last was very feeble.

On January 17, 1924, he developed a severe, general pain in the abdomen with marked tenderness in all its regions and a board-like rigidity of its wall. The temperature rose to 100°F. and slightly above; the pulse rose rapidly and was high. The bowels remained closed and on the 18th he began to vomit fecal matter. His condition, which was bad before the attack started, became steadily worse, and death occurred on January 19, 1924, at noon.

AUTOPSY

The body distinctly emaciated, with no marks or scars on the exterior. The autopsy was limited to the abdomen. Upon opening the latter, there was a moderate amount of dirty-looking liquid in the dependent portions, showing fecal admixture. The appendix was short, thick and tuberculous, but was not perforated.

The gall bladder was about normal in size, the wall somewhat thickened, and there were extensive adhesions to the structures below.

The folds of the intestine everywhere showed a recent exudate, but there was no effort at all at organization, although the folds were slightly bound together. About six feet above the ileocecal valve there was a perforation of the wall of the ileum. The opening, about 3/16 in. in diameter, did not show any effort at repair. The omentum was free from adhesions throughout. The opening communicated with an ulcer on the inner surface, about 3/4 in. in diameter, and there were a few ulcers in the intestine in this region. No ulcers were seen until almost the ileocecal valve; in that region there was slight ulceration.

The caput coli and the ascending colon showed ulceration extending about one foot; none beyond that.

Pathological diagnosis: Tuberculosis of the ileum, appendix, cecum and ascending colon, with perforation of an ulcer in the ileum six feet from the ileocecal valve; chronic inflammation of the gall bladder with adhesions to the adjacent structures; acute peritonitis.

THE PNEUMOPERITONEUM TREATMENT OF TUBERCULOUS ENTEROCOLITIS WITH OXYGEN

Report of a Case[1]

R. L. LANEY

On reading in the *American Review of Tuberculosis* for January, 1924, the report by Dr. Walter L. Mattick of a case of tuberculous peritonitis treated by intraperitoneal injections of oxygen, and the report by Dr. Oscar Monroe Gilbert of a case of tuberculous peritonitis treated by pneumoperitoneum, I am prompted to report the following case of tuberculous enterocolitis which I treated with intraperitoneal injections of oxygen:

A. A. B., white, male, age 30, admitted to Lake Julia Sanatorium on November 19, 1920.

Family History: Mother died of pulmonary tuberculosis 25 years ago. Father and three brothers living and well. One sister died in infancy, cause unknown.

Personal History: Pneumonia at age of 18, duration one month; believes he fully recovered. No other sickness previous to present illness.

Present Illness: Began with hemoptysis in November, 1917, while on active duty as a radio electrician in the United States Navy. He was confined at that time for eight weeks in a hospital at Seattle, Washington. Later he was transferred to the Naval Hospital at Fort Lyons, Colorado, where he remained nine months, being discharged in September, 1918. After this he worked as a telegrapher, until he had another large hemorrhage in November, 1920.

On admission to Lake Julia Sanatorium the patient's temperature (rectal) averaged 100°F. and his pulse was 90. There was a moderate amount of cough, and expectoration amounted to about 3 ounces daily. Bowel movements were normal and digestion was unimpaired. He was 68½ inches tall and weighed 122 pounds. Sputum was positive. Nervous system, urinary tract and voice were apparently normal.

Physical Examination: When I first examined the patient in October, 1921, he presented the usual appearance of a very far advanced case of pulmonary tuberculosis. Weight 124½ pounds, evening temperature 100.4°F.,

[1] From the Lake Julia Tuberculosis Sanatorium, Puposky, Minnesota.

pulse 96. He was coughing a great deal and expectorating about 6 ounces per day. There were large moist râles throughout both lungs, with the exception of the middle portion of the left upper lobe where there was considerable consolidation. There was considerable fibrosis of the upper half of the upper right lobe, and cavitation of both upper lobes. The right isthmus and complemental space were obliterated and the left isthmus and complemental space were greatly narrowed. The fingers were clubbed and cyanotic. The eyes were bright, cheeks flushed and there was considerable dyspnea. Physical examination was otherwise negative.

November 14 and 15, 1921, the patient had hemoptysis amounting to 8 ounces. April 12, 1922, he developed an anal fistula.

Sun-lamp treatment was instituted September 8, 1922, and the patient received daily exposures of the front and back of the chest and abdomen until February 1, 1923, apparently with no benefit. At this time his temperature averaged 100°F. and his pulse was 96. He weighed 150 pounds, but regardless of this gain in weight his tuberculosis had steadily progressed.

February 18, 1923, his evening temperature began to rise at the rate of 0.2° each night, until on February 25 it had reached 101.6°F. For several months the patient had had discomfort after eating, and vague pains in the abdomen. About the first part of February, 1923, he began to have diarrhea to the extent of from 3 to 5 loose bowel movements per day, with considerable abdominal pain. He had had for some time an intense dislike for all kinds of food. He was now coughing very much more than usual and expectorating about 8 ounces per day. Heretofore the patient had been very optimistic but now he had given up hope of ever getting better.

After discussing the matter several days with the patient we decided on February 26, 1923, to give him an intraperitoneal injection of oxygen, with the hope that the procedure would relieve his abdominal distress and diarrhea. The site selected for the injection was in the region of McBurney's point. The skin was painted with tincture of iodine. The skin and all tissues beneath it, including the peritoneum, were anesthetized with a 0.5 per cent solution of novocaine, following the method of R. E. Farr. The apparatus used consisted of a small cylinder of oxygen, a wash bottle and a Brauer-Floyd-Robinson pneumothorax needle. The skin was first punctured with a very small knife and the needle was then pushed through the various tissues until the peritoneum was punctured. We had no means of measuring the amount of oxygen used during this injection, but when we had judged that about 300 cc. had been injected the patient complained of pain in the region of the diaphragm on the right side. The pains were very sharp and at times extended up into the right scapular region.

The oxygen was permitted to flow until the abdomen was quite markedly distended, and the patient complained of feeling very full and of having

considerable of a "belly-ache." The needle was then withdrawn. Immediately upon withdrawal of the needle the oxygen was heard to escape from the puncture. The patient was requested to turn over on to his right side, with the object of having the abdominal viscera drop down to that side and seal the puncture from within. This manoeuvre proved effective at once. The puncture in the skin was then sealed with collodion.

The patient's temperature ceased to rise at once, and with a few variations dropped to 99.6°F. by March 5. On March 8, the patient ate meat for dinner and supper, something that he had been unable to do for a long time.

Immediately after the injection, and for the next three or four days, the patient said that every time he turned from one side to the other he could feel the abdominal viscera fall to the lower side. He said that it was not a painful sensation but that it made him feel a little apprehensive.

He had no bowel movement during the day of the injection, but he had one movement each day for the next three days. On the fourth day he had two bowel movements but no pain. On March 7 the bowel movements were about normal.

On the second day his liking for food returned to a fair extent, and he ate good meals with no pain or discomfort.

During the day of the injection and for the next three days he coughed and expectorated very little, probably on account of the discomfort that the coughing caused in his distended abdomen.

About the fifth day after the injection his cough and expectoration increased to a greater extent than previously. On March 7 cough and expectoration were less than before the injection.

On March 9 the patient was feeling much better than he had felt for many months, but his temperature was 0.2° above normal and he was very anxious to have another injection of oxygen. We decided to comply with his request, and this time we used an artificial-pneumothorax apparatus to measure the amount of oxygen that was injected. We now selected a site on the left side of the abdomen corresponding to McBurney's point and injected 1500 cc. of oxygen. Before starting the flow of oxygen the manometer registered an intraperitoneal pressure of plus one, and after the inflation was completed the manometer registered plus five.

After this second injection of oxygen the patient's temperature varied frequently from 99.4° to 101°F., but it gradually declined and reached its old evening average of 100° by the latter part of July, 1923.

From this time on, until the patient left our institution on August 30, 1923, his intestinal condition was greatly improved. Although he had no very great desire for food, he could and did eat nearly everything that we had on our general diet list. In fact, as far as subjective symptoms and bowel movements were concerned, his intestinal condition was very nearly normal.

On April 22 he was constipated, and was constipated several times after that. We usually gave him two grains of phenolphthalein when he needed a laxative. Once he took 3 drams of magnesium sulphate, and on one occasion he took one dram of fluid extract of cascara.

At this time, about one year from his first injection of oxygen, the patient is still living. He has left the government hospital in Portland, Oregon, and is living at home with his family near that city.

As Doctor Mattick has said, the technique of the operation is very simple. We did not even remove the patient from his bed in one of the wards of our sanatorium. The pneumothorax apparatus and cylinder of oxygen were set up on a small table near the patient's bed. The same needle was used for both inflations.

This method of treatment was suggested to me upon reading in *Minnesota Medicine* for January, 1923, the abstract of a paper written by Dr. John L. Jelks of Memphis, Tennessee, in which he reported the successful treatment of a case of tuberculous enterocolitis by intraperitoneal injections of oxygen.

We have used the pneumoperitoneum treatment with oxygen in two other cases of tuberculous enterocolitis complicating far advanced pulmonary tuberculosis. It was used in both of these cases within just a few days of their deaths with the hope that it might possibly relieve their abdominal distress. Both had been expected to die daily for two or three weeks, and both were suffering intensely with diarrhea and abdominal pain.

Both had such severe cases of tuberculous laryngitis that they could take only liquid nourishment, and very little of that. Naturally, they were in an extreme state of emaciation. The abdomen in each case had the appearance of having the skin draped loosely over the bones. The ribs, the iliac bones and the arch formed by the lumbar vertebrae were very prominent. In both of these cases, to make puncture of the intestines less likely, after the skin had been punctured with the point of a small knife the abdominal wall was pinched between the thumb and forefinger of the left hand and raised as much as possible while a "refill" pneumothorax needle was pushed through into the intraperitoneal space.

One patient, *I. W.*, could only take about 50 cc. of oxygen. He experienced no effect from it one way or another.

The other patient, *O. B.*, managed to take about 400 cc. of oxygen. This small amount of oxygen decreased his diarrhea and greatly relieved

his abdominal distress. In a few days he was very anxious for another inflation; however, death was so imminent that we decided that other means of relief would be more humane.

CONCLUSIONS

Although pneumoperitoneum with oxygen is probably by no means a curative agent in the treatment of tuberculous enterocolitis, it is such a simple and safe procedure that it should be used more frequently on account of the relief that it affords the patient.

For the sake of placing this method of treatment on a more exact basis, an artificial-pneumothorax apparatus should always be used, in order that the amount of oxygen injected can be measured and that the intraperitoneal pressure before and after the inflations may be determined.

Some one, fortunate enough to be situated where cases of tuberculous enterocolitis are fairly numerous, could determine whether the oxygen or simply the increased intraperitoneal pressure is the effective agent, by treating a number of cases with oxygen and a like number with nitrogen at like intraperitoneal pressures.

Whenever possible, in all cases that are followed up until death, an effort should be made to determine the exact pathological changes present.

THE PREVENTION AND TREATMENT OF DIGESTIVE DISORDERS IN TUBERCULOUS PATIENTS[1]

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General Prophylaxis: It has long been recognized that "candidates" for pulmonary tuberculosis are often of the asthenic *habitus* and that they suffer from poor nutrition.[2] It is also well known that malnutrition carries with it particular susceptibility to the disease while good nutrition implies increased resistance. A tragic demonstration of this truth, on a gigantic scale, was recently furnished by the inhabitants of the central European countries who had been subjected to the effects of the blockade during the late war. In these countries the mortality from tuberculosis is said to have increased 100 per cent during the period of privation (1). In view of all this it would naturally follow that one of the most important measures of the general prophylaxis of tuberculosis is the maintenance of a normal level of nutrition among the population at large. It is greatly to be regretted that the need for this is by no means universally recognized. With the exception of school children, on whom the light of medical and sociological publicity has only recently been focused, persons afflicted with malnutrition are not given serious medical attention unless they are actually suffering from the presence of disease. It is not perhaps to be wondered at that such patients do not of themselves seek medical assistance. What is surprising is that physicians as a whole seem rather indifferent. Perhaps this indifference is due to the fact that our attention has of late years been diverted to the dangers of overnutrition. Whatever the cause may be, it can certainly do no harm to emphasize and reëmphasize the fact that malnutrition is not a normal condition, that it always calls for serious treatment and that its conquest is not only a victory

[1] Read at a symposium on tuberculosis before the Yorkville Medical Society, January 21, 1924.

[2] For a recent review of this subject see Bauer, J.: *Die konstitutionelle Disposition zu inneren Krankheiten*, Berlin, Springer, 1921, pp. 67 and 384.

for preventive medicine in general but is a big step in the control of tuberculosis in particular.

Treatment of Malnutrition: It would be a most desirable thing if every malnourished person who either has tuberculosis, is suspected of having tuberculosis or is exposed to tuberculosis were to undergo a complete gastrointestinal survey. This should include a history, a physical examination, the usual stomach tube tests and a routine roentgen examination. Such a study would undoubtedly reveal the frequent presence of certain digestive disorders, the most common of which are ptosis and the asthenic state in general, secretory disorders of the stomach, gastric atony and delayed gastric emptying from any cause, and the various forms of constipation. All these conditions demand attention before the treatment of the malnutrition is even attempted. When one is finally ready to initiate the fattening cure the first step should be the establishment of a specific objective. It is a curious thing that this matter of an objective has not always been clearly envisaged. For example, patients have been fattened as though obesity were a desideratum. The only object of a rational fattening cure is to make the patient attain what would be the normal weight for his age, height and sex. A margin of about ten per cent above this level may be permitted as a factor of safety. The equipment necessary to carry out a successful fattening cure, though simple, is indispensable. It consists of a pair of scales, a measuring rod and a set of standard height-weight tables which may be obtained from any life insurance company or copied from most books on nutrition.

The actual work of fattening a tuberculous subject calls for considerable patience and attention to detail. To begin with, much has been written concerning the anorexia of tuberculosis. As a matter of fact, anorexia is by no means peculiar to the disease in question. It is the general rule, rather than the exception, to have anorexia in malnutrition from any cause. Experience has shown that with proper management good results can be obtained despite the presence of this symptom. Not uncommonly the appetite increases spontaneously soon after the weight begins to go up. It is an old observation, too, that feeble appetite grows with eating,—*l'appetit vient en mangeant*, as the French have it. It is very important, therefore, that the intake of food be judiciously forced from the beginning, and this can only be done by having it at least as carefully supervised as is the consumption of prescribed medication or the administration of any other form of treatment.

In those patients in whom there is fever to contend with it is best to feed most heavily when the temperature is lowest; hence the advantage of making the breakfast the heaviest meal of the day. However, since the object of feeding in fever should be prevention of weight loss rather than actual fattening, the latter may well be left for the afebrile periods.

The question of just what foods to give for fattening tuberculous subjects is hardly so deep a problem as the extent of the writings on the subject might lead one to imagine. In practice it is always a good plan first, to obtain from the patient an exact inventory of what, how and how much he eats. If his selection of foodstuffs is reasonable no change need be made, save urging him to eat as much more of the same things as he possibly can. In some, though not necessarily in all cases, supplementary feedings are of value. The best time for these meals is the mid-morning, the mid-afternoon and the late evening (10 A.M., 4 and 10 P.M.). If all three feedings cannot be taken, one, such as that at bedtime, may suffice for the purpose. Milk is by far the most generally available foodstuff for the supplementary feedings. It may be taken plain or in any of its numerous modifications. A very simple plan is to recommend, in addition to the daily diet, one quart of milk, one-quarter pint of cream and one-quarter pound of butter. If this much more can be taken a rapid gain in weight is bound to follow. It is a wise adviser, however, who keeps in mind the general proposition that a small amount of extra food actually consumed by the patient is worth more than a large amount merely prescribed by the physician. Steady gains in weight have often been initiated by adding so small an amount as one Uneeda biscuit or one tablespoon of cream or one pat of butter to the daily food intake.

How fast should one force the feeding in the effort to make up the weight deficit? Obviously, one must be careful to stop short of inducing signs of gastrointestinal irritation, such as nausea, vomiting and diarrhea. Usually it is a one-sided, rather than a plentiful diet, as such, that produces these symptoms. In general, it is safe to assume that a further increase in food intake is unnecessary as soon as the weight has commenced to climb upward. All efforts at fattening are aided by the avoidance of undue bodily activity. However, whether an absolute bed-rest cure is prescribed or not should depend on individual circumstances.

The fact that a patient may be fattened despite the presence of anorexia does not of course mean that appetite should not be conserved

whenever possible. Among the more important measures directed to this end are:

1: The avoidance of unnecessary medication, particularly by mouth. Fortunately, we are learning to dispense with many useless drugs at the same time as we rely more on physical methods of treatment. To cite but a single instance: consider the superiority of relaxing baths at bedtime to the indiscriminate use of somnifacients in the treatment of chronic insomnia. Another point in this connection is that we should be very careful, particularly in institutional practice, to discontinue promptly the use of drugs once the need for them is over. One sometimes gets the impression that many orders for medication are left standing almost indefinitely.

2: The avoidance of smoking. Tobacco notoriously kills appetite. If its use cannot be stopped altogether it should be strictly restricted to the after-meal period only.

3: Adoption of out-door life. Appetite is often observed to increase in the mountains, at the seaside or out-of-doors in general. In the city, a fresh air cure—now mostly available on roof tops—is a good substitute. In general any change in environment acts as a good appetizer.

4: Care in the preparation and serving of food. Sick people are notoriously dainty eaters. They pick at food, cut away distasteful parts, and so on. It is important that large portions of food be not served at one time for the reason that a small appetite is often discouraged by the mental image of an excessive eating effort. Fat meats being particularly repulsive to tuberculous patients, all fatty, as well as all fibrous portions should be removed in the kitchen. Certain kitchen odors may prove fatal to appetite, as any one can bear witness who has had occasion to travel on shipboard in foul weather. On the other hand, an attractive atmosphere in the broadest sense, a pretty setting of the table, a lively scene from the window, music where possible (even if from a "radio"), and so on, are all subtle stimulants to the entire digestive function.

5: The avoidance of sameness in diet. Lack of variety is incompatible with sustained interest in eating, much as in everything else. This pitfall is particularly to be avoided by those in charge of feeding at institutions for the care of the tuberculous. Every effort should be made to engage the best culinary talent, so as to keep up and encourage the highest possible level of food intake on the part of the patient.

6: Appropriate hydrotherapy and, in special cases, *physical therapy.* These measures are excellent for toning up the entire autonomic nervous system with consequent benefit to the digestion as a whole and the appetite in particular.

The writer has practically never prescribed medicinal appetizers. If such artificial stimulants seem to be needed it is probably much more effective to let the patient select his own condiments (spices, pepper, mustard, horseradish, and so on) to suit his fancy. Authorities are pretty well agreed that, when taken in moderate amounts and in the absence of special contraindications on the part of the digestive tract, the kidneys or other organs, such relishes are probably harmless. In achylia or gastric subacidity the sipping of dilute hydrochloric acid with meals often stimulates the appetite quite sharply.

Dyspepsia of Phthisis; Early Form: The dyspeptic symptoms commonly complained of in early tuberculosis are either reflex in origin or else are due to the toxemia of the disease. Such symptoms are epigastric distress, weight or fulness after meals; hunger distress or pain; heartburn, belching or regurgitation; nausea or vomiting; anorexia and so on, as regards the stomach; and gas distress, bloating, rumbling, increased flatus, colic and irregular bowel action, as regards the intestine. In all such cases there is no organic change in the digestive tract, the symptoms being due to an increased irritability of the stomach and bowel. Inasmuch, therefore, as we are dealing with a functional condition, the principles of treatment applicable to any digestive neurosis apply here as well.[3] Briefly stated, these principles call for rest, general and local, and gradual toning up of the autonomic-nerve control of the digestion. Not only appropriate drugs, but proper psychotherapy, hydrotherapy and physicotherapy must also enter into the treatment.

The treatment of the anorexia has already been described in the previous section. For the annoying "emetic cough," first carefully described by Dettweiler (2), absolute quiet after meals should be insisted upon. Furthermore, the patient's will power should be invoked to resist to the utmost the discharge of the cough and vomiting reflexes, both of which are subject to a certain amount of voluntary inhibition. The swallowing of chipped ice may tend to allay the pharyngeal tickling and thus control the cough in some cases. When this vicious symptom

[3] For a fuller discussion see Kantor, J. L.: *The General Management of Functional Digestive Disorders*, Medical Clinics of North America, Philadelphia, W. B. Saunders Co., 1921, iv, 1537–1551.

has taken a serious hold the use of opiates, and local, pharyngeal and gastric anesthetics may be unavoidable (3).

Gastric Atony and Delayed Gastric Emptying: In advanced stages of tuberculosis the progressive emaciation and toxemia almost regularly bring on atony of the stomach, with stagnation of its contents. There is usually an accompanying anacidity or subacidity. Owing to the unfavorable outlook, a rigorous therapy is out of the question. The most that can be accomplished is probably the following: (1) Prevention of gastric distention by limiting the amount of fluids with meals. As far as practicable a concentrated dry diet should be given as in simple gastric atony. (2) Administration of hot water (about one-half pint) on arising, and otherwise when the stomach is most likely to be empty, as after lavage or occasionally before meals. (3) Aspirations of stagnating contents, followed by brisk lavage, as often as is practicable, which may be only once a week. This relieves nausea, vomiting, regurgitation, heartburn, pain, and gas pressure.

Tuberculosis of the Intestines; Primary Form: Primary tuberculosis of the intestine is now known to be not uncommon in childhood. It may be a part of a more extensive abdominal tuberculous involvement. The prognosis is by no means so dark as in the secondary type of the disease. Careful management over sufficiently long periods gives a fairly large number of therapeutic successes. The writer does not favor surgical intervention in such cases. The medical treatment consists in absolute bed rest and a bland, nonirritating diet. In addition, systematic heliotherapy as practised by Rollier (4) seems to have a favorable influence on the disease. The following case, in which a clinical diagnosis was made of tuberculous enteritis, complicated by tuberculous peritonitis and tabes mesenterica, may prove of interest. Unfortunately, the diagnosis was not confirmed bacteriologically.

Case report: Girl, 11 years old, admitted to Montefiore Hospital, July 25, 1923. Six months before admission, her weight then being 60 lbs., she began to have two or three loose stools a day. Four and one-half months before admission fever came on (101°F.) and the diarrhea increased to four or five green watery stools daily. At the end of May she was admitted to the New York Hospital, where she remained four and one-half weeks. During this period her fever rose to 102° and 103°, she had seven or eight daily stools, bloody at times, and she lost 27 pounds in weight. Proctoscopy showed ulcers running transversely to the axis of the bowel. A diagnosis of tuberculous colitis was made and transfusion of whole blood performed.

On admission to Montefiore Hospital the patient was bedridden and emaciated to the last degree. The skin was of a bronze color. Hemic murmurs were present, the hemoglobin was 65 per cent and the feet were swollen. The pulse was 140. The weight was 33 pounds, that of a three and a half year old child. The abdomen was distended, dull on percussion, and the liver edge was felt two finger-breadths below the costal margin. The spleen was not felt until about a month after admission, when it was found to be moderately enlarged and has been palpable since. There was no fever. The bowels moved four to five times a day, mushy and with a pungent odor. X-ray of the chest was negative for tuberculosis. X-ray of the digestive tract showed distinct defective filling of the ceco-colon. The clinical diagnosis of primary tuberculous colitis was therefore confirmed.

The therapy consisted of (1) bed-rest, (2) bland, fattening diet and (3) heliotherapy,—direct exposure of the abdomen to sunlight for increasing periods up to four hours, divided into two sessions daily.

Course: The patient began to gain weight rapidly. However, the abdomen increased disproportionately in size, and it was soon apparent that the distention was due to rapid accumulation of a fluid exudate. The explanation of this phenomenon was found in Rollier's work, where it was shown that it was a characteristic thing for tuberculous lesions, when first exposed to sunlight, to undergo a reaction manifested by increase in size and other signs of inflammation. The abdomen grew in circumference from $22\frac{3}{4}$ inches on August 14 to $27\frac{1}{2}$ inches on September 23. Paracentesis was considered, but was decided against. At that time the patient was put on the Schmidt intestinal-test diet. This showed the production of stools containing an excess of fat, a finding suggestive of tabes mesenterica. On continuing the Schmidt diet, however, the stools became more formed, reached a neutral reaction, and by the middle of October came down in number to one evacuation daily. The abdomen became suddenly softer after it reached its maximum distention toward the end of September, and by the end of the year it had diminished in girth to 23 inches. Subsequent X-rays have shown a progressive improvement in the colitis. The patient now weighs 65 pounds. Her liver is smaller and the spleen barely palpable. The hemoglobin is normal, as is the pulse. The child is up and about, goes to school and plays just like a normal girl of her age.

Secondary Intestinal Tuberculosis: This is the form usually met with in advanced pulmonary cases. Despite the fact that manifest tuberculous enteritis is commonly regarded as a precursor of a fatal issue in most instances, there is very definite evidence that tuberculous ulcers may heal under favorable circumstances. This evidence is two-fold (5). In the first place, actual signs of healing and unquestioned healed

lesions have been demonstrated by pathological methods. In the second place, intestinal strictures are occasionally observed to result from the healing of tuberculous ulcers. The treatment of secondary tuberculous enteritis is largely a matter of prophylaxis. If this could only be made successful pulmonary tuberculosis would be robbed of one of its chief terrors. The measures available for this purpose, such as they are, are as follows:

1. The swallowing of tuberculous sputum should be avoided. Even if hematogenous or lymphogenous forms of infection do play equal or possibly superior rôles in the etiology, there is no good reason why this precaution should not be taken. The widespread campaign against spitting may do harm in this particular direction unless supplemented by instruction as to proper means of sputum disposal.

2. Hydrochloric acid should be administered in full doses in the subacidity cases. There is some evidence that acid inhibits, even if it does not kill, the tubercle bacillus. It has also been claimed that in anacid cases the intestinal ulcers extend higher up the tract toward the duodenum than they do in fatal cases with normal acidity (6). A very hasty review of some of the Montefiore Hospital autopsy records in which test-meal figures were available seems to confirm this contention. The best way to administer hydrochloric acid is to order it sipped (20 to 30 minims in a half to a glassful of water) during the whole of each meal time.

3. Intestinal stasis should be avoided. The most common localization of tuberculous ulceration is in the terminal ileum and the cecocolon. These are just the portions of the intestine where there is the greatest slowing in the onward passage of the feces under ordinary conditions of health. The probably normal sojourn of material in the former location is 3 to 5 hours; in the latter from 18 to 33 hours. Under certain abnormal conditions affecting this part of the bowel the period of stasis may be much increased. Thus any condition of the distal colon, such as spasm, which tends to hold up the fecal column, will cause a secondary retention of intestinal contents in the proximal colon. This, in turn, may make for ileac stasis. It is therefore of the utmost importance thoroughly to eradicate all forms of constipation in tuberculous patients, in order to prevent ileo-colic stasis and thus to decrease the opportunity for tuberculous intestinal infection. This is obviously not the place to enter into a detailed discussion of the treatment of constipation. It should, however, be emphasized that a thorough under-

standing of the nature of this disorder, as well as of the chief varieties under which it presents itself (atonic constipation, spastic constipation, rectal constipation, redundant colon, etc.), is absolutely essential for success in treatment (7). Unfortunately this particular form of knowledge is as yet not sufficiently widespread among the profession at large.

4. Every case of diarrhea in a tuberculous subject should receive prompt and serious attention. The patient should be put to bed, he should be given a bland well-balanced (not one-sided) diet, and he should have warm applications to the abdomen. In some cases irrigations and possibly transintestinal flushes may be of value. For routine feeding nothing is better than the Schmidt intestinal test-diet which is ideally balanced as to proteins, fats and carbohydrates. Should one of these substances appear undigested in the feces it may safely be assumed that the intestine is incapable of handling that kind of food and that the latter should be excluded from the diet. In this way we should not only be able to bring under ready control all simple (nonspecific) forms of enterocolitis which are by no means uncommon in tuberculosis, but we should also be able appreciably to diminish the chance of superimposing a tuberculous process on top of a simple disorder.

Perirectal Tuberculosis: It is a well-known fact that many perirectal inflammations (fistulae, abscesses, etc.) are due to tuberculosis. The mode of infection is generally assumed to be by swallowed tuberculous sputum which adheres to the rectal mucosa. Ulcers are then formed which break down into the perirectal tissue. For infection to take place in this manner rectal stasis must occur. Normally the feces do not tarry long in the rectum, since the entrance of stool into this part of the bowel is promptly followed by the discharge of the defecation reflex. Under abnormal conditions, however, rectal stasis—dyschezia—does take place. The hard, scyballous masses injure the mucosa and thus the penetration of the tubercle bacilli is favored. It therefore follows that early recognition of rectal constipation and its proper treatment would do much to diminish the chance of tuberculous infection of the rectum and anus.

SUMMARY

1. Malnutrition should be treated among the population at large not only for its own sake but as an effective practical measure to diminish the morbidity of tuberculosis.

2. Every tuberculous dyspeptic should be subjected to a comprehensive gastrointestinal survey as early as possible in the course of the disease.

3. The common digestive disorders should be promptly treated, not only to aid the recovery from the pulmonary disease but to avoid, if possible, the secondary localization of the specific infection in the digestive system.

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THE TREATMENT OF SURGICAL TUBERCULOSIS BY THE LOCAL DIFFUSION OF MERCURY AND ZINC IONS

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In spite of frequent discouragements, accessible tuberculous deposits and abscesses have long been regarded as within the province of surgery; and since the advent of the aseptic era more or less successful surgical intervention has even been extended to tuberculous joints—the touch-me-nots of the older surgeons. Latest and boldest of the efforts in this line is the inclusion of tuberculous cavities within the chest in the surgical field, with a hopeful promise, Eloesser and Brown (*Am. Rev. Tuberc., February, 1924, viii, 519*) and Lovelace (*Journ. A. M. A., February 9, 1924, 459*) having opened several such cavities, the latter applying chemotherapy within the cavities.

The fact that the surgery of tuberculous tissues differs from those more normal, in possessing a lowered healing reaction, may not be the only explanation of the larger percentage of failures after curettement or excision. Another element may be the ease with which living bacilli may be reimplanted in tissues specially favorable to their growth. If this last assumption be well founded, it is evident that a surgical means by which the bacilli could be devitalized during removal and the absorbents sealed would advance the treatment of surgically situated tuberculosis in all parts of the body.

Such considerations induced the writer to employ what might be called electrochemical curettage (ionic curettage) as long ago as 1899, in the treatment of persistent and intractable tuberculous abscesses in the neck, with such quick healing and small resultant scars that the patients were exhibited to the members of the Philadelphia County Medical Society in the winter of 1900–1901. Since then some twenty other cases, several in rather a desperate condition, have been subjected to the same treatment. A recent follow-up inquiry into the present condition of these patients has shown that all are well without exception, there having been no relapses or development of other tuberculous conditions.

The simple procedure described when these patients were shown twenty-three years ago is still used without modification. Such excellent time-tested results would seem to commend it to the attention of orthopedic surgeons and special workers in tuberculosis for a wider test.

The purpose of the method is the devitalization of the infected neoplastic material *in situ* by the anodic diffusion of the ions of mercury and zinc. An ordinary galvanic current is used. A zinc probe of a size adapted to the extent of the growth or cavity is amalgamated with quicksilver, connected with the anode of the power generator, and passed gently into the cavity after an opening has been made, if none be already present, and the circuit is completed by a large cathodic pad on a distant skin surface. When the current is gently turned on, the probe is eroded and the ions of both metals are formed and driven into the tissue in contact with the instrument, the former appearing whitened as it is devitalized. The microörganisms of secondary infections, incidentally, are also destroyed by the same sterilizing ions, a purulent discharge being changed at once to a serous one, with which the white, crumbly debris later is extruded from the cavity. Such an application seals the capillaries, lymphatics and lymphatic spaces at the edge of the devitalized tissue for several days, at the end of which time it is repeated and extended if the first application was not sufficient to destroy all infected tissues.

It has seemed, in the limited experience indicated, best not to attempt to destroy all infected tissues at once, for these microörganisms are not malignant, and triweekly ionizations with mild, almost painless currents have not only seemed sufficient for the devitalization, but appear to add an additional element of stimulation of the reparative energies of the surrounding tissues. This is inferred from the appearance of both local and general improvement after the first week of treatment and long before the destruction of the whole of the infected tissues. Another advantage of the repeated use of weak currents is that blood-vessels seem to be immune to weak doses of these cauterant ions while tuberculous tissue, being an unusually good conductor, takes most of the current and consequently the ions. The treatment of large deposits or abscesses situated in vascular regions is therefore as bloodless as that of the smallest node in a nonvascular region. The method is equally effective in eroded bone tissue, but with a deferred separation of the bone sloughs.

During this treatment the general health improves steadily and noticeably. The time required for the cavity to fill in with healthy granulations and heal from the bottom varies from six weeks to several months, according to the gravity of the case, the ionizations being made weaker and less frequently as healing progresses.

The technical details of zinc-mercury ionization in surgical tuberculosis have been given elsewhere in full, together with most of the case reports (*vide* appended bibliography), but I may say that they are within the ready accomplishment of any office practitioner who possesses a good controller and meter for the use of the galvanic current and some facility in their use. The controller and meter are to be used for the smooth and painless turning on of the required power from either a direct current dynamo of the usual medical voltage or from a battery of dry cells. A 45-volt radio B battery is an excellent source of the power for temporary installation or for portable use. The ionic dosage is a product of the strength of the current and of its duration. The doses employed by the writer varied from three to seventy-five milliamperes for fifteen to thirty minutes.

Where sterilization rather than tissue destruction has seemed desirable the mercury ion has been employed alone, diffused from an amalgamated gold anode.

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A BACTERIOLOGIGAL STUDY OF A CASE OF CLINICAL TUBERCULOSIS IN WHICH THE TUBERCLE BACILLUS COULD NOT BE DEMONSTRATED IN THE SPUTUM[1]

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An average of the statistics for the year 1921 of the New York City tuberculosis clinic and of two sanatoria shows, in over 9,000 cases diagnosed as pulmonary tuberculosis, that the tubercle bacillus was demonstrable in the sputum of only 46 per cent or rather less than half the total number. It is readily understood that in incipient cases foci not connected with a bronchiole may exist, or lesions may be more or less walled off, and that in such cases the causal agent does not find its way into the sputum. In some of the moderately advanced cases, however, and in a few far advanced, the classical acid-fast microörganism is not contained in the expectoration, although frequently the clinical examination and X-ray findings point to a probable open lesion. That the exciting agent should be absent from the sputum of such cases appears incredible. It would seem rather that the sputum had been insufficiently examined, or that the tubercle bacillus may be present in an aberrant form not demonstrable by our present methods of examination, or that a tuberculous condition, *pseudotuberculosis*, caused by another microörganism, exists more frequently than is generally supposed.

Probably the first to describe pseudotuberculosis were Mallassez and Vignal (1). They were able to give rise to their *tuberculose zoogleique* by inoculating animals with a nodule obtained from the arm of a child who had died with tuberculous meningitis. The tubercles formed resembled those of true tuberculosis; they showed even the same epithelioid and giant cells. They did not contain the Mycobacterium of Koch, but zooglea formed by cocci, isolated or in chains, which were not acid-resistant. Passage of the tuberculous material through a series of guinea pigs produced similar lesions in the inoculated animals. In their first publication the authors state that in their opinion a relationship exists between

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their *zoogloées* and the Mycobacterium of Koch. In a second paper published a year later they (2) conclude that there is "no real identity."

Eberth (3) observed, in a rabbit dying spontaneously, nodules in the liver, spleen and kidneys, in the centre of which appeared masses of short thick microörganisms nonresistant to acid and sometimes forming chains like those of Malassez and Vignal. Eberth did not cultivate the microorganism but believed it to be identical with that of the two previously mentioned authors.

Pfeiffer (1888), Nocard (1889), Zagari (1889), and Parietti (1890) record very similar findings. Each of these observers isolated a microorganism which he regarded as the causal factor of the disease. Priesz (4), after comparing the cultural and pathogenic characters of these four microörganisms, decided that they were identical.

Much (5), in 1907, working with apparently tuberculous material, found, instead of the typical rods, many granules which were demonstrable only by Gram's method of staining. Inoculation of this material into the peritoneal cavity of a guinea pig resulted in an exudate which at the end of forty-eight hours showed, in addition to the granules, some slender non-acid-fast rods. In the fluid withdrawn after seventy-two hours many of the rods were found to be acid-fast. As a result of this and other experiments, Much, believing that he was working with the Mycobacterium of Koch, concluded that the microörganism passes through three stages in its development, namely, transition from the granular form to the non-acid-resistant bacillary form and further to the acid-fast Ziehl-staining rod.

Maher (6) described a microörganism obtained originally from barn scrapings, with which he was able to produce tuberculous lesions in guinea pigs and, because of its pleomorphism, he assumed that he was dealing with the Mycobacterium of Koch in a hitherto unrecorded development of its life cycle. He noted variation in acid-resistance, the transformation of the typical rods into granular, filamentous, coccoid and spore forms; also the development of a symplastic stage. Of the recovery of the microorganism from inoculated animals he states,

> I have, with proper precautions, taken bits of the fresh spleen of infected guinea pigs and dropped them into tubes of sterile milk. In twenty-four hours the tubes were filled with non-acid-fast cocci which soon became diplococci and then biscuits and then gave place to non-acid-fast granular rods larger than tubercle bacilli, but resembling them in shape and in the disposition of the granules.

Three days later he found in these same tubes the non-acid-fast rods transformed into what he names his *Bacillus maternus*. He continues, "This new organism was at least ten times as large as the tubercle bacillus; it occurred in chains and single and was the largest bacillus I have ever seen. It contained much granular spore matter of varied shape and some of this spore matter was consistently acid-fast." He found that his microörganism digested but did not curdle milk, that it produced spores and that it liquefied gelatine. It seems very probable that it was closely related to or was identical with that to be described later in this paper and not, as he supposed, the classical Mycobacterium of Koch.

Numerous cases, presumably tuberculous, have been reported more recently from which so called "diphtheroids" have been isolated; other cases have been attributed to a streptothrix. Hoag (7), studying general paresis and certain conditions of the lungs, cultivated 199 diphtheroids, the majority of which were from the lungs and respiratory tract. He considered 146 of these to be identical. Walker and Adkinson (8), in a bacteriological examination of the sputum of 49 cases of bronchial asthma, isolated in 35 instances apparently the same type of diphtheroid. They describe it as extremely pleomorphic and consider it a new type.

Members of the group have been isolated from, and have been considered the causal agent of other diseased conditions somewhat related to tuberculosis. Kedrowski (9) and others have cultured from leprosy lesions diphtheroids to which they have assigned definite causal properties, each regarding his culture as a stage in the life cycle of the Hansen bacillus. The lymphadenopathy known as Hodgkin's disease has been ascribed by Fraenkel and Much (10) to a diphtheroid type of microörganism. Bunting and Yates (11) have reported similar findings. Negri has applied the name *Corynebacterium granulatis maligni* to the diphtheroids isolated from cases of Hodgkin's disease.

As regards the streptothrices, the literature on the subject contains a large number of case reports and detailed descriptions of the pathological findings. Unfortunately, few of these case reports are accompanied by cultural studies. Among the conditions making a study of this group difficult are the diverse opinions and practices as to nomenclature. Several generic names have been, and still are, used by different authors, such as *Actinomyces*, *Discomyces*, *Nocardia*, *Streptothrix*, *Oöspora*. According to the classification of the Society of American Bacteriologists all of the above are included in one genus, *Actinomyces*. The genus is described as consisting of species "growing in the form of a much-branched

mycelium which may break up into segments that function as conidia, etc. *Endospores are not produced.*" Foulerton (12), on the other hand, studying a large number of strains, describes the type form as

> a tangled mass of branched mycelium. The mycelial stage is followed by segmentation and fragmentation producing bacillary forms and, in artificial media, by chain sporulation. A process similar to this is also probable in isolated rod segments. Old cultures show bacilli long, short, wavy, diphtheroid and paired, and isolated spores. All are strongly Gram-positive and look like bacilli and cocci. They may be acid-fast or not.

Since some species of the Genus *Bacillus* will, under certain conditions, show all of the above characteristics, the question arises as to whether some member or members of this group have been responsible for many of the reported cases of streptothricosis and pseudotuberculosis, and even of those allied conditions from which diphtheroids have been isolated. Probably, as suggested by Claypole (13), the reason so few cultural studies have been made on the reported cases is due less to the inability of the causal microörganism to grow than to failure to identify it in its bacillary form.

The above statement of Claypole has been amply verified in this laboratory. On numerous occasions, when endeavoring to obtain the tubercle bacillus by a cultural method from sputum in which it could not be demonstrated microscopically, instead of the Mycobacterium of Koch, pure cultures of non-acid-fast rods were obtained. Such cultures were discarded since the absence of acid-resistance or branching seemed to preclude their relationship to the forms usually associated with tuberculosis. The frequency of the occurrence, however, suggested the possibility that such microörganism might be either the Mycobacterium of Koch in the non-acid-fast form described by Much and others, or an independent microörganism giving rise to a pseudotuberculosis indistinguishable clinically and roentgenographically from true tuberculosis.

A microörganism which was obtained on six different occasions by the method described by Petroff (14) from the sputum of a patient diagnosed as tuberculous, but in whose expectoration the Mycobacterium of Koch had never been found, was used as the basis of a study to determine (1) cultural characteristics, (2) etiological significance and (3) classification.

A smear preparation from the culture showed slender rods solidly stained or with polar granules similar to *C. diphtheriae*; sometimes three

to five granules were seen within the rod. The bacillary form seemed to preclude, for a time, any possible relationship to the streptothrices; rather did a kinship to tubercle bacilli seem evident, since at times a slight degree of resistance to decolorization by acid was observed.

The patient, a Japanese, aged 35 years, complained of general lassitude, loss of weight, a catching sensation in the region over the sternum and a cough which had been more or less troublesome for about a year. The doctor who examined him made a diagnosis of pleurisy and sent him to the sanatorium. On admission a clinical examination showed the following condition: *Right lung:* Percussion note impaired above 2 R and 4 v.s.; a few fine râles above clavicle. *Left lung:* Percussion note impaired above 2 R and 3 v.s. and below 7 v.s. A few râles heard above clavicle and above 3 v.s. Breath sounds very faint 7 to 9 v.s. and absent below 9 v.s. A few fine râles heard at level of 7 v.s. *Report of roentgenographical examination: Right side:* Slight infection throughout with possible slight activity above and below clavicle; definite early infiltration from 2 i.s. to 4 R. *Left side:* Active infiltration at apex to 3 v.s. decreasing in intensity to 3 i.s. Thickened pleura over side, effusion at base. Weight 103½ lbs. No history of tuberculosis in family. Temperature 99.4°. *Diagnosis:* Moderately advanced tuberculosis, AII.

I. STAINING, MORPHOLOGICAL, CULTURAL AND BIOCHEMICAL CHARACTERISTICS OF THE ISOLATED MICROÖRGANISM

1. Resistance to decolorization; Gram staining: As a preliminary, the degree of resistance to the common decolorizing agents at different periods of growth and when grown on different media was determined; also the reaction to Gram's stain.

Bienstock (15) found that non-acid-fast microörganisms could be made acid-resistant by cultivation on a medium containing butter. Ritchie (16), on the other hand, concludes that most bacteria which are not acid-proof cannot acquire this property by growth on a fatty medium. He states, however, that the power of resisting acid but not alcohol was restored to a bacillus formerly acid-proof by growth on a fatty substance. Wherry (17), studying the development of a "saprophytic culture of *B. tuberculosis*" in various synthetic media, observed that the microorganism could be rendered non-acid-fast by continual growth unfavorable to the synthesis of fat. He also noted that a return to the acid-fast condition could be brought about by supplying such substances as acetates as a source of carbon and nitrogen, or from various ammonium salts and propyl alcohol. The presence of certain phosphates, and especially potassium di-hydrogen phosphate, appeared to accelerate the process.

In the present work, accordingly, the influence of butter and of the formula used by Wherry was studied by culturing the microörganism

on the following media: (1) Petroff's medium; (2) the same medium plus a thin film of butter poured over the slant;(3) the same medium except that the beef juice was replaced by the solution used by Wherry; and (4) galactose agar on the surface of which 0.5 cc. of Wherry's solution was placed.

The cultures were incubated at 37°C. and smear preparations made at the end of 7, 14, 21, and 28 days. They were stained by (1) Ziehl-Neelsen method, using 5 per cent hydrochloric acid in distilled water for one minute as the decolorizing agent; (2) Ziehl-Neelsen method, using 95 per cent alcohol as the decolorizing agent for one minute; and (3) Gram's method (Nicolle's modification).

For the most part the microörganisms did not retain the carbol-fuchsin stain; they were, however, more resistant to the acid than to the alcohol. A number of acid-fast microörganisms could frequently be seen, together with others partially or wholly decolorized. Butter did not noticeably affect their resistance, nor did the solution used by Wherry. In smear preparations from the three egg media the results were more or less constant; whereas on agar, by the end of the second week, most of the rods had been replaced by spore-like bodies which were quite resistant to both acid and alcohol. Young forms were strongly Gram-positive; older ones showed less ability to retain the dye.

A strain of tubercle bacillus cultured on the various media remained constant both in morphology and resistance to the decolorizing agents used; very little growth occurred on the galactose agar.

2. Morphology: The marked pleomorphism of the microörganism and the fact that spore formation occurred only on an agar medium suggested a possibility of contamination and the advisability of repeating the experiment. A second attempt to isolate the microörganism proved successful, and the new strain was cultivated with practically the same result.

PLATE 1

Fig. 1. Growth on egg medium. Solidly stained and granular rods, single or in pairs. Single stain.

Fig. 2. Growth on egg medium. Rods, and spindle-shaped bodies with deeply stained granules in centre. Single stain.

Fig. 3. Growth on egg-meat medium. Filaments and branching forms. Single stain.

Fig. 4. Growth on egg medium. Diphtheroid forms. Single stain.

Fig. 5. Growth on agar and on egg medium. Presymplastic stage. Single stain.

Fig. 6. Growth on agar medium. Granular filaments, with granules enlarged when in juxtaposition with another filament. Single stain.

Plate 1

Smears from the egg medium showed solidly stained or granular rods usually in pairs and with the ends in apposition (fig. 1). Frequently single rods appeared with bipolar granules, which tended to approach each other until they resembled diplococci; sometimes heavy clubbed forms with deeply stained centres (fig. 2) or long wavy branched forms appeared (fig. 3). At other times a resemblance to the diphtheroid groups was marked (fig. 4). By the fourth week the microörganisms showed a tendency to arrange themselves in long parallel rows which at intervals appeared to fuse together, forming a mass in which the individual rods were not discernible (fig. 5). Such masses were frequently only faintly stained, particularly in the centre; their appearance was suggestive of the symplastic stage described by Löhnis (18). By the fifth week individual rods again predominated. Even after eight weeks' growth no spore-like forms were observed in the smears from cultures grown on egg medium.

Preparations from agar showed quite a different picture. In young cultures short rods predominated. Frequently long slender undulated forms with granules at regular intervals, which seemed slightly larger than the width of the rod, were noted. Occasionally two of these slender threads approached each other and remained side by side; in such instances the granules appeared to have greatly enlarged and extruded from the side of one filament to connect it with the second filament. After a short space the second thread curved away from the first, perhaps to join in like manner a third (fig. 6). By the end of the first week many short rods had developed clubbed ends which later appeared as exospores, the rod gradually shortening until only the spore remained. By the end of the third week only a few slender threads remained in a field of oval spores. The spores seemed to be of two distinct types, one small, elliptical and intensely stained, the other oval, less solidly stained and possessing an envelope.

Morphology seemed thus to be largely determined by the substrate. Transferred from egg medium to agar the microörganism developed in the manner typical for that medium. Its descendents, returned to egg medium again, appeared in the forms characteristic of growth on egg medium.

An attempt was made to follow the development of these spore-like bodies by transplanting a loopful of an old agar culture to (1) a tube of egg medium and (2) a tube of agar, and then making smear preparations from the outer portion of the growth at two-hour intervals. On egg medium at the end of two hours the deeply staining bodies had lost their

acid-resistance, took the counterstain and became more elongated; a few showed signs of dividing and assumed a diplococcoid form. In the four, six and eight-hour periods further development occurred, until, by the end of ten hours, most of the small, solid, elliptical bodies had passed through the diplococcoid form to slender non-acid-fast rods, arranged for the most part in pairs with their ends in apposition (fig.7). No development was noted of the less solidly stained exospores, which appeared as numerous at the end of ten hours as at the beginning, but more faintly stained.

On agar the deeply fuchsin-stained elliptical bodies developed as rapidly as on egg medium; also, a few of the spores at the end of two hours showed a short protrusion near one of the poles. At the end of four hours these protrusions had developed into rods, many of which were still attached to the spore envelope (fig. 8). At the end of ten hours the microscopic field showed nothing but vegetative forms, either as single rods or in pairs with their ends in apposition.

The microörganism was isolated from six specimens of sputum obtained from the patient at different times. On the fifth occasion a development occurred which had not been noticed in previous cultures. At the end of three days a smear preparation, made from a scarcely visible growth on egg medium, showed the typical non-acid-fast rods. On the sixth day growth was sufficient to make a subculture; a smear preparation made at this time revealed, instead of the microscopic picture seen a few days before, only a few of the slender rods, and long parallel lines of large non-acid-fast streptobacilli, containing at irregular intervals intensely stained acid-fast bodies (fig. 9). The acid-fast bodies had no constant size or shape; some were barely visible, while others were so large as to occupy almost the whole cell. Frequently one entire microörganism in the series of segments appeared acid-fast, while its neighbor on each side remained non-acid-fast.

A transplant was made to agar and daily smears prepared from both the original egg tube and the subculture. Preparations from the egg medium showed the acid-fast bodies taking an even more amorphous form and a massing together of the microörganisms until they appeared as more or less rounded bodies, both acid-fast and non-acid-fast, somewhat resembling closely packed yeast cells or irregular stones in a wall (fig. 10). Some of these showed a tendency to fuse, become indistinct and result in small nests of the usual non-acid-fast slender rods (fig. 11).

The agar subculture began at once to revert to the type of growth typical on agar medium. By the tenth day the smear preparation showed only a few non-acid-fast bacilli and many spores and small solidly staining acid-fast bodies. A similar but less marked phase in the development of the first isolated culture was subsequently observed (fig. 12) and also in several members of the aerobic spore-forming group grown at the same temperature (37°C.).

3. Heat resistance: Comparison of the growth on egg and agar media: A suspension in saline solution of a three weeks' growth on egg medium consisting of non-acid-fast rods, and a similar suspension of a three weeks' growth on agar consisting mainly of spores, were heated to 85°C. Subcultures were made from each suspension on both egg and agar medium at the end of 30, 45, 60 and 90 minute periods. None of the microorganisms from the egg medium survived exposure to heat for 30 minutes, while growth appeared on every tube inoculated from the spore-containing suspension from the agar medium. Daily smears made for one week from the tubes inoculated at the end of 60 minutes' heating showed the usual development, namely, bacillary forms on egg medium and spore formation on agar.

4. Cultural and Biochemical Reactions:

Gelatin Stab Culture: 22°C. Filiform growth along line of puncture most abundant at top. Liquefaction apparent on 6th day; depth of liquefaction on 30th day, 20 mm.

Nutrient Broth: 22° and 37°C. Surface ring growth, some sediment with few flakes adhering to side of test tubes.

Potato: 22° and 37°C. Growth light brown, moist, glistening.

PLATE 2

Fig. 7. Growth on egg medium. Development of small elliptical acid-fast bodies to non-acid-fast diplococcoid forms and to granular or solidly stained rods.

Fig. 8. Growth on agar medium. Development of spores shown as unstained oval bodies. Single stain.

Fig. 9. Growth on egg medium. Stage in life cycle of fifth strain isolated. Streptobacilli with acid-fast granules and segments (black).

Fig. 10. Growth on egg medium. Development from streptobacilli to irregular granules and to acid-fast yeast-like forms (black).

Fig. 11. Growth on egg medium. Development from yeast-like acid-fast forms to solid and diphtheroid forms.

Fig. 12. Growth on egg medium. Solid and granular forms and giant spiral forms with acid-fast granules (black).

Note: Apparent granulation in some of the figures does not represent real granules, but merely light staining.

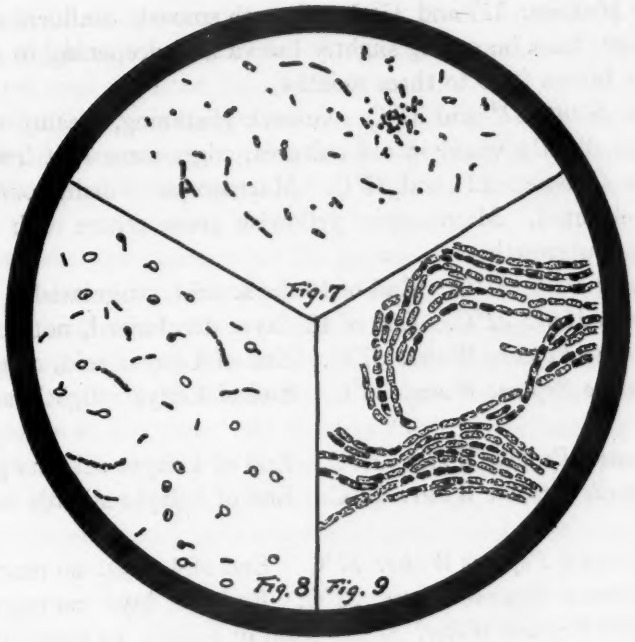

Plate 2

Egg Medium: 22° and 37°C. Growth smooth, confluent and colorless at first, later becoming slightly brown and deepening to an almost chocolate brown (two to three months).

Agar Slant: 22° and 37°C. Growth glistening, creamy white and confluent; slightly viscid in old cultures; edges somewhat irregular.

Agar Colonies: 22° and 37°C. Macroscopic: Small, round, white, slightly elevated. Microscopic: yellowish green centre with small anthrax-like outgrowth.

Litmus Milk: 37°C. End of 10 days: acid, coagulated.

Litmus Milk: 22°C. End of 10 days: decolorized, not coagulated.

Dextrose Peptone Water: 37°C. End of 4 days: acid, no gas.

Dextrose Peptone Water: 22°C. End of 4 days: slightly acid, no gas.

Mannite Peptone Water: 37°C. End of 4 days: acid, no gas.

Mannite Peptone Water: 22°C. End of 4 days: slightly acid, no gas.

Saccharose Peptone Water: 37°C. End of 4 days: no reaction.

Saccharose Peptone Water: 22°C. End of 4 days: no reaction.

Lactose Peptone Water: 37°C. End of 4 days: no reaction.

Lactose Peptone Water: 22°C. End of 4 days: no reaction.

Maltose Peptone Water: 37°C. End of 4 days: slightly acid, no gas.

Maltose Peptone Water: 22°C. End of 4 days: no reaction.

When newly isolated, growth occurred on egg medium at the end of three to five days and rarely on agar. After several transplants, development took place almost equally well on both media. Growth at 37°C. was always more rapid and abundant than at 22°C.

II. ETIOLOGICAL SIGNIFICANCE

1. Allergic reaction: To the routine tuberculin test, namely, the intracutaneous injection of 0.001 mgm. of old tuberculin followed in case of no response by 0.1 mgm., the patient failed to react. A third injection seven days after the first, of 0.1 mgm., produced an inflamed area about 15 mm. in diameter which did not appear until after twenty-four hours and which disappeared in ninety-six hours.

Some weeks later a Pirquet test was made, using a preparation analogous to old tuberculin, in which the newly isolated microörganism had been grown in place of the Mycobacterium of Koch. Following is the result:

Patient: In six hours an inflamed area about 15 mm. in diameter appeared, which within twenty-four hours became markedly indurated. A pigmented area persisted for several months.

Controls: Two nontuberculous members of the staff: no reaction. One tuberculous patient with positive sputum: no reaction. One patient diagnosed tuberculous with negative sputum: very slight reaction.

2. *Pathogenicity for guinea pigs:* Six guinea pigs were inoculated with a saline suspension of the microörganisms grown on culture medium; one with an emulsion of the liver of the first guinea pig showing definite lesions, and one with a culture of the microörganism recovered from the liver. None of the animals showed any sign of decreased activity or loss of appetite at any time. At autopsy small hemorrhagic spots were apparent in the liver of each of the inoculated pigs, as well as minute gelatinous foci in the lungs. Sections of the lungs, liver and spleen were examined microscopically by a recognized pathologist. Following is the report:

GUINEA PIG	SITE OF INOCULATION	INOCULUM	KILLED	EXAMINATION OF TISSUE SECTIONS
			weeks	
1	Groin	1 cc. light suspension from egg medium	4	*Liver:* Three small focal necroses in the parenchyma, which contain fragments of nuclear material *Lungs:* A nodule, 4 or 5 mm. in diameter, which appears to be of granulomatous character, containing multinucleated cells of a type similar to that seen in a tuberculous lesion
2	Abdominal cavity	2 cc. light suspension from egg medium	8	Not significant of any marked infection. Small foci of alveolar exudate which consist largely of eosinophilic cells
3	Abdominal cavity	Emulsion of liver of guinea pig 1	8	In addition to varying degrees of atelectasis, there are some pus cells in a few of the bronchi and occasionally in the alveoli. The picture is that of a normal lung
4	Abdominal	1 cc. light suspension of microörganisms recovered from liver of guinea pig 1	8	Report the same as for 3

GUINEA PIG	SITE OF INOCULATION	INOCULUM	KILLED	EXAMINATION OF TISSUE SECTIONS
			weeks	
5	Heart	2 cc. heavy suspension from agar (mainly spores)	2	*Liver:* Minute focal necroses *Lungs:* Small lesions beneath the pleura consisting of lymphocytic accumulations of irregular shape *Spleen:* Slight degeneration of the contents of the large Malpighian corpuscles
6	Heart	2 cc. medium suspension from egg medium (vegetative forms)	2	Changes less evident than in guinea pig 5. A small hemorrhage is seen beneath the pleura in the lung section, which may be an indication of an embolic process. Both guinea pigs show evidence of infection by a microörganism of slight virulence, while the reaction in the lung of guinea pig 5 is distinctly lymphocytic
7	Heart	Same as for 5	4	Not distinctly abnormal
8	Heart	Same as for 6	4	*Lungs:* Peripheral hemorrhages with fading of the alveolar walls, characteristic of small infarcts. At the borders of these hemorrhages there are also very small rounded accumulations of closely packed lymphocytes. These may be hypertrophied normal lymphoid follicles of the lung or they may be small granulomatous lesions
9	Control			Normal
10	Control			Normal

While the lesions produced in the inoculated animals were comparatively slight, their nature seems to have sufficiently resembled those of true tuberculosis to suggest a possibility of similar more massive lesions in man being diagnosed as tuberculous.

Of special interest was the report of an excessive number of eosinophiles in the tissue sections. The cells were packed with minute round bodies and frequently small masses of such bodies were seen apparently free.

The question suggested itself as to whether the reported eosinophiles were possibly the *zoogloées* of the earlier writers and the granular remains of the injected microörganisms. Löhnis (19), discussing the observations of various writers, states

> The large metachromatic granules . . . . will have to await a more correct classification. The same holds true concerning those metachromatic granules which were found in and outside of *Mastzellen* and were classed as metabolic products by Bayum (1903) as well as by Guilliermond and Mawas (1908). That some of them may be gonidia or regenerative bodies of bacteria is just as well possible, as was the case with the round bodies seen by Hibler in and outside of the *Mastzellen* accompanying the bacilli of symptomatic anthrax.

In the case under consideration, evidence seems to point to a similar theory, namely, that the cells in the tissue sections reported as eosinophiles might in reality have been stationary cells laden with bacterial granules, since a differential blood count of the patient from whom the microörganism was obtained, and also of an inoculated guinea pig, showed only a normal eosinophilic content, namely, two to three per cent.

III. CLASSIFICATION

The regularity with which spore formation occurred on agar, together with the fact that the segmented bacillary forms were more frequently seen than branching filamentous forms, indicated a possible relationship to the aerobic spore-forming bacilli; in any event, the ability to form spores excluded the microörganism from the Family *Actinomycetaceae* which, as has been already observed, includes the Genus *Streptothrix*. Accordingly, six available cultures of aerobic bacilli were subjected to the same conditions used in the cultivation of the unknown microörganism, namely, growth on egg medium and on agar at 37°C. Smear preparations made at the end of 3, 7 and 14 days showed decided variation in morphology.

MICROÖRGANISM	DAYS GROWTH ON MEDIUM		MORPHOLOGY
	Egg	Agar	
	days	*days*	
B. mycoides	3		Long non-acid-fast filaments with irregular deeply stained acid-fast portions
	7		Mainly large irregular acid-fast masses
	14		Similar
		3	Very slender interwoven non-acid-fast filaments with pin-point acid-fast granules
		7	Similar
		14	Similar
B. subtilis	3		Non-acid-fast bacillary forms
	7		Similar but showing tendency to form symplastic masses
	14		Similar
		3	Long bacilli showing some autolysis
		7	Some granular forms, many long interlacing filaments with occasional apparent branching
		14	Similar
B. megatherium	3		Heavy non-acid-fast bacilli, some autolysis
	7		Forms more irregular, many sausage-shaped
	14		Similar
		3	Non-acid-fast rods
		7	Irregular forms, some spores
		14	Similar
B. cereus	3		Very granular, acid-fast long interlacing filaments
	7		Less granular and shorter filaments
	14		Fine blue granules and irregular acid-fast masses
		3	Granular and solidly stained bacilli
		7	Many spores and solidly stained oval acid-fast bodies
		14	Similar
B. mesentericus	3		Short rods, clubs and bacilli with acid-fast granules
	7		Similar; irregularities more marked
	14		Similar; many of the bacilli with acid-fast granules arranged radially
		3	Diphtheroids, clubs and rods with acid-fast polar granules
		7	Solidly stained rods, many spores
		14	Similar

MICROÖRGANISM	DAYS GROWTH ON MEDIUM		MORPHOLOGY
	Egg	Agar	
	days	*days*	
B. prowsnitzi	3		Curved, acid-fast filaments and streptobacilli; some spiral forms
	7		Similar, but slightly acid-fast
	14		Slender, lightly stained filaments and free irregular acid-fast bodies
		3	Long slender threads and irregular masses, some acid-fast, others taking the counter-stain
		7	Similar
		14	Slender lightly stained filaments and irregular free acid-fast bodies

Visible spore-formation did not occur in any of the six microörganisms when grown on egg medium at incubator temperature and only in three cultivated on agar, namely, *B. megatherium*, *B. cereus* and *B. mesentericus*. While there undoubtedly are species which produce spores freely on egg medium at 37°C., it appears that some of the well-known aerobic bacilli do not have that ability. This fact, combined with their pleomorphism may probably have led to their classification at times as diphtheroids.

Although none of the above microörganisms showed quite the same morphology as the newly isolated strain, there seemed sufficient similarity to suggest a close relationship. Spore formation under identical conditions was taken as indicative of the closest relationship. Of the three answering to this test, *B. megatherium* was discarded because of its morphological dissimilarity and its marked proteolytic action on egg medium. *B. mesentericus* was apparently the most closely related. In order to establish the identity of the microörganism, if possible, with one of the already known members of the group, a request was sent to several laboratories for cultures of *B. mesentericus* and closely related strains. Following is a comparison of the biochemical reactions of those received, together with *B. cereus*, a different strain of *B. subtilis* and the newly isolated microörganism.

The table on page 460, while it does not prove the identity of the microorganism with any one of those with which it is compared, does reveal several points of resemblance between it and the group, namely, liquefaction of gelatine, reaction on milk, nonproduction of indol and nonproduction of gas in the sugar media used.

MICROÖRGANISM	SPORE FOR 14 DAYS		PROTEOLYSIS	DEXTROSE		MANNITE		SACCHAROSE		LACTOSE		MALTOSE		GELATINE			INDOL	LITMUS MILK 10 DAYS
	Egg	Agar		A	G	A	G	A	G	A	G	A	G	Puncture	Liquefaction	Depth in 30 days		
Temperature 37°C.:																		
B. mesentericus 726	−	+	±	+	−	+	−	+	−	−	−	−	−				−	Slightly acid, coagulated
B. mesentericus A. M.	−	+	+	+	−	+	−	+	−	−	−	−	−				−	Slightly acid, coagulated
B. mesentericus B	−	+	+	+	−	+	−	+	−	−	−	−	−				−	Slightly acid, coagulated
B. vulgatus	−	+	+	+	−	+	−	+	−	−	−	+	−				−	Slightly acid, digested
B. niger	−	+	±	+	−	+	−	+	−	+	−	+	−				−	Decolorized, coagulated
B. sherens	−	+	±	+	−	+	−	−	−	+	−	+	−				−	Acid, coagulated
B. aterrimus	+	+	+	+	−	+	−	+	−	−	−	+	−				−	Decolorized, digested
B. globigii	+	+	±	±	−	±	−	±	−	±	−	±	−				−	Unchanged
B. subtilis	+	+	±	+	−	+	−	+	−	−	−	+	−				−	Decolorized, coagulated
B. cereus	−	+	±	+	−	+	−	+	−	−	−	+	−				−	Slightly acid, coagulated
B. x	−	+	±	+	−	+	−	−	−	−	−	+	−				−	Slightly acid, coagulated
Temperature, 22°C.:																		
B. mesentericus 726	−	+	−	+	−	+	−	±	−	−	−	−	−	Filiform	4	35	−	Decolorized, coagulated
B. mesentericus A. M.	−	+	−	+	−	+	−	+	−	−	−	−	−	Filiform	2	35	−	Decolorized, not coagulated
B. mesentericus B	−	+	−	+	−	±	−	±	−	−	−	−	−	Filiform	3	35	−	Decolorized, coagulated
B. vulgatus	−	+	−	+	−	+	−	+	−	−	−	±	−	Filiform	2	35	−	Decolorized, slightly coagulated
B. niger	−	+	−	+	−	+	−	−	−	±	−	+	−	Filiform	1	35	−	Decolorized, slightly coagulated
B. sherens	−	+	−	+	−	+	−	−	−	±	−	+	−	Arborescent	1	35	−	Decolorized, slightly coagulated
B. aterrimus	+	+	±	+	−	+	−	+	−	−	−	±	−	Filiform	2	35	−	Decolorized, slightly coagulated
B. globigii	+	+	±	±	−	−	−	−	−	−	−	−	−	Filiform	4	20	−	Unchanged
B. subtilis	+	+	±	+	−	+	−	+	−	−	−	+	−	Filiform	8	20	−	Decolorized, not coagulated
B. cereus	−	+	±	+	−	+	−	−	−	−	−	+	−	Arborescent	2	35	−	Decolorized, slightly coagulated
B. x	−	+	−	±	−	±	−	−	−	−	−	−	−	Filiform	6	20	−	Decolorized, not coagulated

Another interesting point brought out is the fact that growth is evidently more abundant and reactions more marked at 37° than at 22°C., although the optimum temperature for the group is usually considered to be midway between the two points.

That a slight degree of acidity was noted in the milk tubes in some instances, and not in the lactose fermentation tubes, may be explained by the fact that in the latter the reaction was set at pH 7.8 and the readings were made at the end of four days, whereas the initial reaction of the litmus milk was less alkaline and the final readings were made at the end of ten days.

As regards morphology, many common features were noted: polar granules and diplococcoid forms in the strains of *B. mesentericus;* deeply stained acid-fast elliptical bodies on agar in *B. mesentericus*, *B. niger*, *B. cereus*, and *B. subtilis;* very marked irregularity in form and degree of acid-resistance in *B. cereus*, *B. Prowsnitzi*, *B. sherens* and *B. mycoides;* long interlacing filaments in most, and occasional branching in *B. cereu* and *B. subtilis*.

Thus it would seem that acid-fastness and branching which have been more or less accepted as specific for Actinomyces and related microorganisms are by no means restricted to this so called higher order, but are quite common under certain conditions among members of the aerobic spore-forming group. A table compiled by Löhnis (19) shows that true branching has been actually observed with representatives of all groups of the bacteria.

Even among the species already classified as higher bacteria, it appears difficult to place a line of demarcation between the mold fungi on the one hand and the true bacteria on the other. Claypole (20), with a view to classification, studied morphologically, culturally and serologically, ten different streptothrices, together with *B. leprae* and the human type of tubercle bacillus. She found it impossible from any point of view, morphological, biological or serological, to draw a sharp dividing line in the series. At one end of the group was a distinctly non-acid-fast mycelial growth and at the other end a bacillary and completely acid-fast growth, while between the two extremes several intermediate types were found showing bacillary fragmentation and partial acid resistance. The one extreme seemed to lead so surely toward the hyphomycetes and the other just as surely toward the true bacteria that she is led to put the question: By what right are we including in one genus such apparently divergent forms as spore-bearing mycelium and an acid-fast bacillus?

She finds an answer to the question and an explanation of this perplexing pleomorphism in the assumption that the hyphomycetes and the true bacteria are each specializations from an ancestral streptothrical type, since in the latter may be found many of the characteristics more markedly developed in the former.

If this hypothesis be accepted, the aerobic spore-forming bacilli would logically be considered as intermediate between the streptothrices and the bacteria, since they have retained the ability to form spores and under certain conditions a degree of acid-resistance and a tendency to branch. It is but a step further to assume that, a biological relationship being established, a similarity in pathogenicity may exist and that certain members of the group may have been responsible for some of the cases diagnosed as streptothricosis or pseudotuberculosis from which branching forms and diphtheroids have been isolated. Although many members of the *B. mesentericus* group are distinctly saprophytic, so also are many of the streptothrices, and so also are many of the acid-fast bacteria. It seems quite conceivable, therefore, that among such a large number of species, pathogenic types other than *B. anthracis* exist and that they may be responsible for many of the conditions resembling tuberculosis in which the Mycobacterium of Koch cannot be demonstrated.

CONCLUSIONS

1. Certain of the aerobic spore-forming bacilli will, when cultivated on egg medium at 37°C., exhibit the pleomorphism and varying degrees of acid-resistance characteristic of the streptothrices.

2. Under the above conditions they lose their ability to form spores and at times so closely resemble *C. diphtheriae* that it is conceivable that diphtheroids isolated from various pathological conditions may belong to this group.

3. A member of the *B. mesentericus* group appears in this instance to be the causal agent of a pseudotuberculosis indistinguishable clinically and roentgenographically from true tuberculosis.

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THE SKIN-SENSITIZING PROPERTY OF TUBERCLE BACILLI MADE NON-ACID-FAST BY TREATMENT WITH OLEIC ACID OR OLIVE OIL

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The anaphylactic state may be induced in guinea pigs by injections of filtered aqueous extracts of tubercle bacilli (Baldwin (1), Austrian(2)), but the skin of guinea pigs receiving this treatment is not hypersensitive to intracutaneous injections of tuberculin. The author (3) has obtained weak tuberculin responses in guinea pigs injected with filtered exudate taken from the peritoneal cavity of tuberculous guinea pigs. The peritoneal exudate consists of the contents of the cavity removed twelve to twenty-four hours after the intraperitoneal injection of a large quantity of a heavy tubercle-bacillus suspension. Petroff (4) has obtained weak tuberculin reactions in guinea pigs treated with filtrates containing the nucleoprotein fraction of extracts of tubercle bacilli. So far as has been determined, no one has reported the production, by injection of Berkefeld filtrates, of skin reactions approaching in severity those so regularly elicited in the tuberculous guinea pig.

The results obtained with dead tubercle bacilli appear to lack uniformity. Roemer (5) treated guinea pigs with killed cultures and found that about half of the animals showed slight local reactions to tuberculin while the other half showed no skin sensitization. Petroff (4), on the other hand, has found in guinea pigs treated with dead bacilli a response qualitatively and quantitatively like that of the tuberculous animal.

Table 1 presents 10 guinea pigs from a total of 35 that received intraperitoneal or subcutaneous injections of heat-killed tubercle bacilli. In 7 of the 25 not tabulated varying quantities of old tuberculin were injected along with the dead bacilli. After about three weeks most of the animals gave some degree of hyperemia and induration at the site of the intracutaneous test. In certain animals, such as nos. 267 and

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TABLE 1

NUMBER	WEIGHT OF BACILLI IN EACH DOSE (1)	DATES OF INJECTIONS				RESPONSE TO THE INTRACUTANEOUS TUBERCULIN TEST (2)			
	mgm.	*1922*				*1922*			
225	4	May 23, i. p. (3)				June 14, doubtful			
226	40	May 23, i. p.				June 14, doubtful			
227	2	May 23, i. p.				June 6, doubtful			
		1922	*1922*	*1922*		*1922*			
232	2	June 9, i. p.	June 13, i. p.	June 17, i. p.	June 20, i. p.	June 28, negative	July 6, weak		
234		July 3, i. p.	July 5, i. p.	July 7, i. p.	July 10, i. p.	July 17, weak	July 25, weak		
								1923	*1923*
267	60	Oct. 2, subc. (4)	Nov. 1, subc.			Oct. 21, weak	Dec. 18, weak	Jan. 22, weak (5)	Feb. 15, weak (5)
268	60	Oct. 12, subc. (4)				Oct. 21, doubtful	Dec. 18, weak	Feb. 15, weak	
							1923		
269	4	Nov. 4, i. p.	Nov. 6, i. p.	Nov. 8, i. p.	Nov. 10, i. p.	Dec. 17, doubtful	Jan. 21, weak	Feb. 15, weak	
270	15	Nov. 4, subc. (4)	followed by 14 doses of same size during next month					Jan. 21, weak (5)	Feb. 15, weak (5)
273	3	Dec. 5, subc. (4)	Dec. 6, subc.	Dec. 7, subc.	Dec. 9. subc.	Dec. 18, weak			

Notes: (1) The suspensions consisted of washed glycerin-broth cultures, in distilled water and heated in the Arnold sterilizer for one hour. To filter paper placed in a desiccator for two weeks 1 cc. of the suspension was added and the increase in weight determined after a second desiccation of one month.

(2) The test consisted of the injection of a sufficient quantity of a 1 to 5 dilution of old tuberculin to raise a bleb about 8 mm. in diameter.

(3) *i. p.* signifies intraperitoneal.

(4) *Subc.* signifies subcutaneous.

(5) Weak signifies a non-necrotic reaction, but in these instances the swelling and hyperemia were unusually prominent.

270 of table 1, the tuberculin reactions consisted of areas of hyperemia and induration measuring 2 cm. across, but in none of the 35 was actual necrosis of the skin noted. Tuberculin appears not to influence the effect of the killed tubercle bacilli when it is administered at the same time or subsequent to the dead-bacillus injections.

Cultures of tubercle bacilli, dehydrated with alcohol and brought into contact with oleic acid which has been shaken vigorously with a few drops of water, become non-acid-fast to a very considerable extent. The method of obtaining this effect of the oleic acid has been described in a previous report (6). It consists in decanting the 14-day growths from two 100-cc. Erlenmeyer flasks to one larger flask, decanting the bouillon and covering the growth with 100 cc. of alcohol for one minute. In instances in which the biuret test has been made on the filtrate the growth has been washed with 100 cc. of water before dehydration. The alcohol is quickly decanted and the sedimented bacilli covered with 10 cc. of oleic acid (*Merck U. S. P.*) which has been shaken vigorously with 4 drops of water. After several days at 37°C. most of the bacilli have become non-acid-fast.

Since a few acid-fast bacilli tend to persist in cultures treated in this way, the only certain method of determining the antigenic property of non-acid-fast bacilli seemed to be the preparation of a filtrate which contains the non-acid-fast forms in solution. It was found that filtrates containing dissolved bacilli, as shown by the biuret reaction, have the property of sensitizing the skin of guinea pigs to tuberculin. However, in the preparation of many filtrates it has been determined that this antigenic activity may be greatly lessened or entirely destroyed by varying the technique. That oleic acid is a local irritant when injected into the tissues is to be considered in the preparation of the filtrates. The oleates when well diluted are less irritating.

The animals in table 2 received injections of five different filtrates. Except for variations in the amount of alcohol used for precipitation and the quantity removed afterwards, the preparation is as follows: The cultures of two flasks are incubated for one week in a flask, in contact with oleic acid after being dehydrated. To the flask are added 100 cc. of 95 per cent alcohol and after 15 minutes about 75 cc. of the supernatant clear liquid is decanted. Seventy-five cubic centimetres of alcohol are then added and after 5 minutes the clear liquid is removed with a pipette, leaving about 15 cc. of sediment in the flask. About 50 cc. of 0.2 per cent sodium hydrate and two drops of phenolphthalein

TABLE 2

NUMBER	INJECTIONS OF FILTRATE			RESPONSE TO INTRACUTANEOUS INJECTIONS OF TUBERCULIN			REMARKS
	1923						
309	Sept. 29, 5 cc., subc.	Oct. 11, 5 cc., subc.	Oct. 16, 5 cc., subc.	Oct. 18, mild	Nov. 26, 3 mm., mild	Nov. 7, mild	Killed Feb. 13, 1924, no lesions found
311	Oct. 4, 13 cc., subc.			Nov. 1, 4 mm., mild	Nov. 21, 5 mm., mild	Dec. 26, 5 mm., mild	Killed Jan. 29, 1924, no lesions found
312	Oct. 9, 5 cc., i. p.	Oct. 13, 5 cc., i. p.	Oct. 16, 2.5 cc., subc.	Nov. 1, mild	Nov. 8, 2 mm., mild		Killed Feb. 13, 1924, no lesions found
320	Oct. 23, 5 cc., subc.	Oct. 27, 5 cc., subc.	Nov. 1, 2 cc., subc.	Dec. 13, slight, mild			
				1924			
345	Dec. 18, 15 cc., subc.			Jan. 8, 2 mm., mild	Jan. 16, 2 mm., mild		

are added to bring the reaction near the neutral point. The flask is placed at 37°C. for twenty-four hours and shaken occasionally. . The contents are passed through a 5 × 1 inch type V Berkefeld filter. The filtrate gives a faint biuret test. Most of the oleic acid is removed with the alcohol before neutralization, but there is sufficient sodium oleate in the filtrate to render it quite irritating. All animals injected with filtrates prepared in this way have given mild positive tuberculin reactions.

Acetone precipitates the bacilli when added to the incubated bacillus-oleic acid mixture in the same way that alcohol does. When 75 cc. of acetone (*U. S. P.*) are added to the mixture a voluminous precipitate

TABLE 3

NUMBER	INJECTIONS OF FILTRATE				RESPONSE TO INTRACUTANEOUS INJECTIONS OF TUBERCULIN	
	1923	*1923*	*1923*	*1923*	*1923*	*1923*
324	Nov. 6, 4 cc., i. p.	Nov. 12, 3 cc., i. p.	Nov. 16, 4 cc., i. p.	Nov. 20, 4 cc., subc.	Dec. 16, negative	Dec. 20, negative
325	Nov. 6, 4 cc., i. p.	Nov. 12, 3 cc., i. p.	Nov. 16, 4 cc., i. p.		Dec. 16, negative	Dec. 16, negative
						1924
340	Nov. 28, 4 cc., i. p.	Dec. 1, 4 cc., i. p.	Dec. 4, 4 cc., i. p.	Dec. 6, 4 cc., i. p.	Dec. 12, negative	Jan. 3, negative
341	Nov. 28, 4 cc., i. p.	Dec. 1, 4 cc., i. p.	Dec. 4, 4 cc., i. p.	Dec. 6, 4 cc., i. p.	Dec. 12, negative	Jan. 3, negative

at once forms and may be separated by filtration through filter paper or an alundun cone. Washing the precipitate on the filtrate with an additional 75 cc. of acetone removes the oleic acid quite completely. If the washed precipitate is placed in the incubator for two days with about 20 cc. of 0.2 per cent sodium hydrate, a Berkefeld filtrate is obtained which gives a very marked biuret test but which, when injected into guinea pigs after neutralization of the slightly alkaline solution with dilute acetic acid, does not sensitize to tuberculin (table 3).

If a sodium hydrate solution of 0.02 per cent instead of 0.2 per cent is used the Berkefeld filtrate gives a doubtful or negative biuret test and does not sensitize to tuberculin (table 4).

It appears therefore that incomplete removal of the oleic acid and its subsequent neutralization with dilute alkali facilitate the solution of

TABLE 4

NUMBER	INJECTIONS OF FILTRATE				RESPONSE TO INTRACUTANEOUS INJECTIONS OF TUBERCULIN	
	1923				*1924*	*1924*
346	Dec. 22, 15 cc. subc.				Jan. 3, negative	Jan. 16, negative
	1924	*1924*	*1924*	*1924*		
353	Jan. 10, 5 cc., subc.	Jan. 12, 2 cc., subc.	Jan. 15, 2 cc., subc.	Jan. 18, 2 cc., subc.	Jan. 26, negative	

TABLE 5

NUMBER	INJECTIONS OF FILTRATE	RESPONSE TO INTRACUTANEOUS INJECTIONS OF TUBERCULIN	
	1924	*1924*	
351	Jan. 2, 4 cc., subc.	Feb. 13, mild	
			1924
357	Jan. 28, 20 cc., subc.	Feb. 13, doubtful	Feb. 27, mild
358	Jan. 28, 20 cc., subc.	Feb. 13, doubtful	Feb. 27, mild
359	Jan. 30, 15 cc., subc.	Feb. 13, negative	Feb. 27, mild
360	Feb. 4, 10 cc., subc.	Feb. 27, mild	
363	Feb. 8, 10 cc., subc.	March 8, mild	

the non-acid-fast bacilli. The alkali has no effect on the persisting acid-fast bacilli, and untreated cultures covered with 0.2 per cent sodium hydrate for four months stain acid-fast. On the other hand, most of

the oleic acid must be removed, on account of its irritant properties when injected. The partial removal of oleic acid with acetone instead of alcohol (table 5) yields results confirming those presented in table 2. The 6 guinea pigs were injected with five different filtrates containing, after neutralization, varying amounts of sodium oleate. In guinea pigs 360 and 363 most of the oleic acid was removed by decanting the bacillus-oleic acid mixture into an alundun cone and filtering without suction. The alundun cone was then placed in a beaker containing 25 cc. of water and normal sodium hydrate added in small quantities during two to three hours, to neutrality to phenolphthalein. The contents of the beaker were placed in an Erlenmeyer flask and, after forty-eight hours at 37°C., passed through a type V filter. The same procedure was followed in preparing the filtrates injected into guinea pigs nos. 351, 357, 358 and 359 except that the bacillus-oleic acid mixture was diluted with two volumes of acetone before filtration through the cone.

CULTURES OF TUBERCLE BACILLI DEHYDRATED WITH ALCOHOL OR ACETONE AND TREATED WITH OLEIC ACID

Cultures rapidly dehydrated with alcohol or acetone soon show characteristic changes when placed in the incubator with oleic acid containing a few drops of water in suspension. At the end of one hour there is no demonstrable change; at the end of four hours about 10 per cent are non-acid-fast, while smears made after twenty-four hours show at least one-half to have lost their acid-fastness and to present granular disintegration. After several days to a week or more there still remain a few acid-fast bacilli which tend to persist indefinitely. The evidence now at hand indicates that these as well as the non-acid-fast forms are not capable of infecting guinea pigs (table 6).

Since cultures treated in this way appeared not to infect guinea pigs they were injected into a larger series, to determine their effect on skin sensitiveness to tuberculin (table 7). Most of the oleic acid was removed before injection. In my experience these were the first uninfected animals to react to tuberculin with a centimetre of necrosis at the site of the test. The lesions became more severe during the second and third day, persisted for five days to a week and healed with scar formation. Since the suspensions injected contained a few acid-fast bacilli the animals were examined for infection. An examination of the animals of table 6 showed that the acid-fast as well as the non-acid-fast forms contained in suspensions prepared from cultures incubated in oleic acid

TABLE 6

NUMBER	MATERIAL INJECTED	AUTOPSIES
299	July 28, 1923, injected into groin with 0.1 cc. of dehydrated culture incubated for 8 days with oleic acid	Nov. 2, 1923, chloroform. *Autopsy:* Groin and internal organs normal
301	July 28, 1923, injected into groin with 0.1 cc. of dehydrated culture incubated for 8 days with oleic acid	Nov. 2, 1923, chloroform. *Autopsy:* Groin and internal organs normal
308	Sept. 26, 1923, injected into groin with 1 cc. of heavy suspension prepared as for 299 except oleic acid removed with alcohol	Nov. 3, 1923, chloroform. *Autopsy:* A 3 mm. lymph node in groin; internal organs normal. Ground lymph node in mortar and injected 321 and 322
321	Nov. 3, 1923, injected into groin emulsified lymph node from guinea pig 308	Jan. 29, 1924, chloroform. *Autopsy:* Groin normal; internal organs normal
322	Nov. 3, 1923, injected into groin emulsified lymph node from guinea pig 308	Jan. 29, 1924, chloroform. *Autopsy:* Groin normal; internal organs normal.

TABLE 7

NUMBER	DOSAGE	RESPONSE TO INTRACUTANEOUS TUBERCULIN TEST (1)	
361	Feb. 6, 1924, injected subc., 5 cc. aqueous suspension of culture 7 days in contact with oleic acid (2)	Feb. 23, 1924, severe with slight necrosis	March 7, 1924, severe with 4 mm. necrosis
362	Feb. 6, 1924, ditto, heated in Arnold for one hour	Feb. 23, 1924, doubtful	March 7, 1924, mild
364	Feb. 18, 1924, injected subc., 5 cc. suspension of culture 6 days in contact with oleic acid (3)	March 8, 1924, severe with 8 mm. necrosis	March 14, 1924, severe with small ulcer at centre
365	Feb. 18, 1924, ditto, heated in Arnold for one hour	March 8, 1924, negative	March 14, 1924, negative
366 to 374 inclusive	Feb. 26, 1924, injected subc., 5 cc. suspension of culture in contact with oleic acid 7 days (4)	March 7, 1924, nine positive	March 15, 1924, all positive and two with slight necrosis

Notes: (1) *Mild* indicates hyperemia and induration only, while the reactions with definite necrosis are designated as severe.

(2) At the end of 7 days the culture-oleic acid mixture was diluted with acetone, filtered through paper and the bacilli on paper washed with acetone.

(3) Excess of oleic acid removed by pouring the culture-oleic acid mixture into an alundun cone before incubation.

(4) Removal of oleic acid before incubation by pouring the culture-oleic acid mixture into an alundun cone.

were dead. Guinea pigs 362, 364 and 371 (table 7) were chloroformed at the end of forty-two days or more after injection. Careful examination of the groins where injections were made and of the internal organs showed 1 to 3-mm. lymph nodes in the groins which appeared to be normal. Smears of these nodes showed no acid-fast bacilli. On the other hand, in guinea pigs receiving groin injections of heat-killed suspensions acid-fast bacilli were found in smears of lymph nodes eighty-eight days after injection.

Animals injected with suspensions of treated cultures heated in the Arnold sterilizer for one hour showed little reaction to tuberculin.

CULTURES OF TUBERCLE BACILLI DEHYDRATED WITH ACETONE AND TREATED WITH OLIVE OIL

At the time of the first experiments to determine the effect of oleic acid on cultures dehydrated with alcohol, olive oil was added to dehydrated cultures with the result that the bacilli stained perfectly after a contact with the oil of a week or more. Later it was found that olive oil produced changes in cultures dehydrated with acetone, although without effect after alcohol dehydration. The effect on the staining and morphology of the bacilli was the same as that obtained with oleic acib; that is, at the end of a week at 37°C. the great mass of culture had become non-acid-fast, except for an occasional rod which retained its acid-fast property. The evidence at hand indicates that the few acid-fast forms which persisted do not infect animals and were probably not viable at the time the olive oil was added. Guinea pigs have been injected with the olive oil-treated cultures to determine whether animals are infected and whether the skin is sensitized to tuberculin (table 8).

It is necessary to dehydrate the cultures carefully. The bouillon is decanted completely from a flask containing a growth of two weeks which covers the surface of the medium and 75 cc. of acetone (*c.p.*) added to the mass of culture in the flask. The flask is rotated at intervals to hasten the dehydration. After about five minutes the acetone is decanted completely and the growth covered with 10 cc. of pure olive oil which has just been shaken vigorously for several minutes with one or two drops of water. The flask is rotated to mix the growth and oil and then placed at 37°C. The growths from a number of flasks (ten) have not been successfully combined before the dehydration.

The response to the intracutaneous tuberculin tests of 23 guinea pigs (table 8) injected with olive oil-treated bacilli was severe in every instance. The reactions persisted from four or five days to a week and healed with scars at the site of the tests. Frequently the necrosis was very distinct and ulceration has followed. Three of the guinea pigs (375, 379 and 387) were chloroformed and autopsied five weeks after the injections. Although the examination of these animals did not conclu-

TABLE 8

NUMBER	DOSAGE	TUBERCULIN RESPONSE
375 376 377	March 4, 1924, injected subc., 2 cc. of culture-olive oil suspension (1)	March 18, 1924, mild. March 24, no. 375 severe with necrosis. Autopsy Apr. 11
379 to 386 inclusive	March 6, 1924, injected subc., 1 cc. of culture-olive oil suspension (2)	March 18, 1924, no. 379 mild. March 24, 379 severe with necrosis. March 31, 379 severe with ulceration. Autopsy April 11
387 388 389	March 6, 1924, injected subc., 2 cc. of culture-olive oil suspension (3)	March 18 and 24, 1924, no. 387 severe with necrosis. Autopsy Apr. 11
390 to 394 inclusive	March 6, 1924, injected subc., 1 cc. of culture-olive oil suspension (4)	March 31, 1924, no. 392 severe with ulceration
395 396 397 398	March 11, 1924, injected subc. 2 cc. of culture-olive oil suspension (5)	March 31, 1924, no. 395 severe with slight necrosis

Notes: (1) Culture dehydrated in usual way with acetone, incubated for 6 days with olive oil. Injections subcutaneously in groins and axillas.

(2) Incubated with olive oil 7 days. The 8 guinea pigs received about one-half the growth from five flasks.

(3) Contact with oil 3 days.

(4) Contact with oil 6 days.

(5) Contact with oil 5 days.

sively exclude infection, no evidence of infection was found. Number 375, chloroformed five weeks and three days after the injection, showed in both groins perfectly translucent lymph nodes, measuring 1 to 4 mm. in diameter. On the right, there was a clear cystic cavity, 2 by 5 mm., containing clear oily fluid. Number 379 showed in both groins fibrous masses, 5 by 7 mm., which contained small translucent lymph nodes. In no. 387 a break appeared in the skin of the left groin on the fifth

day. At autopsy this opening was perfectly healed and the tissue of the groin contained only one or two normal lymph nodes. In the right groin there was a thin-walled cyst, containing a clear oily fluid, in which there were small white flakes. These consisted of amorphous material but showed no acid-fast bacilli. Smears from the lymph nodes of the three animals showed no acid-fast bacilli. The peritoneal and thoracic organs were perfectly normal.

DEHYDRATED CULTURES OF TUBERCLE BACILLI TREATED WITH LIQUID PETROLATUM

To obtain with petrolatum oil an action on cultures like that of olive oil it was necessary to dehydrate carefully. With complete dehydration about three-fourths of the bacilli became non-acid-fast within a week. In order to dehydrate, a sufficient amount of acetone to sediment the culture was added to one flask with a growth of two weeks. The liquid was decanted and the growth covered with 50 cc. of acetone for about ten minutes. The acetone was decanted and the culture at once covered with 10 cc. of liquid petrolatum vigorously shaken with two drops of water. Incubation was at 37°C.

DISCUSSION

In a previous report on the effect of oleic acid on tubercle bacilli it was suggested by the writer (6) that the change of the bacilli to non-acid-fast rods was possibly due to a metabolic product or enzyme produced by the living bacilli, since the effect was not noted in cultures killed by heat. A similar action of olive oil and petroleum oil strengthens this view. In the case of olive oil the failure of the reaction in cultures dehydrated with alcohol and the success of the reaction in ones dehydrated with acetone indicate that it is essential to obtain an intimate encasement of the bacilli in the oily medium. The alcohol (95 per cent) and the olive oil do not mix to any extent. while acetone and the oil mix in all proportions. Acetone and liquid petrolatum do not mix in all proportions. This may explain the less perfect action of the liquid petrolatum. Whether the medium in which the bacilli are suspended is oleic acid, olive oil or liquid petrolatum, a minute quantity of water in fine suspension in the medium is an essential factor in the reaction. Kendall, Day and Walker (7) have demonstrated the formation of a lipase by tubercle bacilli, while Corper and Sweany (8) have shown autolytic

and proteolytic enzymes to be present. The inference is that suspension of the dehydrated bacilli in an oily medium tends to confine the metabolic products closely to the microöganism. Furthermore, cultures undergo no change at a temperature of 4°C. but, when removed from the refrigerator after twenty-four hours and placed at 37°C., the loss of acid-fastness proceeds in the usual way.

Whether oleic acid, olive oil, or petroleum oil is used there are a few acid-fast bacilli which tend to persist. The non-acid-fast forms may be dissolved in dilute alkali, and a Berkefeld filtrate obtained from the solution which has the property of inducing a slight amount of skin hypersensitiveness to tuberculin when injected into guinea pigs. Injections of the tubercle bacilli themselves (acid-fast and non-acid-fast) treated with oleic acid sensitize much more strongly the skin of guinea pigs, so that necrotic focal lesions develop where the tuberculin is injected.

The evidence presented in tables 6, 7 and 8 makes it quite certain that dehydration, exposure for one week to oleic acid at 37°C. and removal of excess of oleic acid kill the bacilli. Cultures treated with olive oil have the same microscopic appearance, and the preliminary experiments consisting of the autopsy of three guinea pigs (nos. 375, 379 and 387) five weeks after injection indicate that the bacilli are likewise killed by contact with olive oil. It has been noted frequently that cultures one month to several months old give a greater number of persisting acid-fast bacilli than the younger cultures ordinarily employed. Since the occasional acid-fast bacilli that persist are dead at the time animals have been injected with the mixtures containing them, it seems likely that they are not affected for the reason that they are dead at the time the oleic acid or olive oil is added.

The results recorded have been obtained with cultures of H37, a human strain of the tubercle bacillus which has a moderate virulence for guinea pigs but which always produces progressive lesions and ends fatally.

CONCLUSIONS

1. Cultures of tubercle bacilli dehydrated with alcohol become, when incubated with oleic acid containing traces of water, non-acid-fast except for an occasional acid-fast bacillus which tends to persist indefinitely. Cultures dehydrated with acetone, on incubation with olive oil containing traces of water, undergo the same change.

2. The skin of guinea pigs injected with the filtrates, containing the non-acid-fast bacilli dissolved in dilute alkali, reacts mildly without local necrosis to the intracutaneous injection of tuberculin.

3. The skin of guinea pigs injected with the oleic acid-treated tubercle bacilli suspended in water after removal of the excess of oleic acid with alcohol reacts to tuberculin with local necrosis and ulceration. Such suspensions contain only dead tubercle bacilli.

4. The skin of guinea pigs injected with incubated olive oil-tubercle bacillus mixtures reacts to tuberculin with necrosis and ulceration. Autopsies of guinea pigs five weeks after injection indicate, but do not conclusively prove, that such suspensions contain only dead tubercle bacilli.

5. The necrotic ulcerative tuberculin reaction, so readily elicited in tuberculous guinea pigs by the intracutaneous injection of old tuberculin into the skin, has not been seen in a series of animals treated with heat-killed tubercle bacilli. The property of sensitizing the skin to tuberculin, possessed by cultures incubated with oleic acid or olive oil, is largely lost when the incubated cultures are heated for one hour in the Arnold sterilizer.

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HEMATOLOGICAL STUDIES IN EXPERIMENTAL TUBERCULOSIS OF THE GUINEA PIG[1]

III. PROTEIN CONCENTRATION OF THE BLOOD SERUM AND ERYTHROCYTE VOLUME IN TUBERCULOUS GUINEA PIGS

STUDIES IN THE BIOCHEMISTRY AND CHEMOTHERAPY OF TUBERCULOSIS. XXXII

LAURETTA BENDER AND LYDIA M. DEWITT

In the first paper of this series (1) the following results were reported in experimental chronic tuberculosis:

A chronic tuberculosis developed in 13 guinea pigs which received relatively light inoculations and showed a prolonged resistance to the disease (see no. 8, chart 1, no. 14, chart 2 and no. 5, chart 3 of the original paper). These animals lived nine months or more after the inoculation.

The most striking change in the blood picture was the marked fluctuation of all the elements. These fluctuations were seen in the erythrocytes and their hemoglobin content, the total leucocyte count and the individual leucocyte counts such as the neutrophils, lymphocytes and eosinophils. There seemed to be a tendency for all the elements to fluctuate together in the larger variations although smaller variations in the individual elements occurred by themselves. There are also undoubtedly other factors at work on the blood picture, such as leucocytic reactions to secondary infections, eosinophilia, etc. But, allowing for such factors, the blood picture suggests the possibility that the variations are not due to absolute increases and decreases in the total number of cells of the animal but to relative changes because of variations in the blood concentration or plasma content of the blood. As the guinea pigs did not have hemoptysis, night sweats or diarrhea, this apparent change in blood concentration cannot be due to these factors, but must be related to some such factor as that suggested by the work of Gaertner and Roemer (2), who showed that the products of the tubercle bacilli when extracted

[1] From the Otho S. A. Sprague Memorial Institute and the Department of Pathology, University of Chicago.

and injected into dogs caused an increased lymph flow. (See also discussion by Petersen (3) and his co-workers on changes in endothelial permeability.) These marked fluctuations we believe to be the most significant part of the blood picture in chronic tuberculosis. The condition demands further study, not only to determine the underlying causes, whether they be due to secretogogue action of the products of the infection or lesions, to changes in the permeability of the blood capillaries or changes in the osmotic pressure of the blood, but also because it explains the great diversity of opinions as to blood changes that occur in tuberculosis, especially when conclusions are drawn from one count or a few isolated counts.

This phenomenon was noticed by some of the early clinical workers. Sokowloski (4) and Applebaum (5) reported variations in the red-blood-cell count, with frequent increases of the erythrocytes above normal, and they suggested that this might be due to profuse sweating, expectoration and diarrhea. There was no definite evidence offered to defend either suggestion except the work of Gaertner and Roemer (2), but as these workers did not attempt to free their tubercle bacilli extracts of extraneous proteins the specific secretogogue action of the bacilli or their products is still open to question.

The constant fluctuation in the blood curves in our hematological studies on chronic tuberculosis in the guinea pig offers some proof that variations do occur in the blood volume and concentration. It seemed worth while to confirm these indications with some other experimental work. Blood volume estimation suggested itself as the most direct means. But none of the methods, not even the improved vital red technique, is feasible in guinea pigs which we wish to keep alive in as nearly normal a condition as possible for a long period of time. It was thought that some information of a similar nature might be gained by determining the protein concentration of the serum together with cellular counts and hematocrit readings. Accordingly the following experiment was planned.

Guinea pigs with typical chronic tuberculosis were examined. These pigs were so inoculated that it was expected that they would live at least nine months after inoculation, show the typical cellular fluctuations of the animals with chronic tuberculosis previously examined by us, and show tuberculous lesions at autopsy. The following examinations were made on the same specimens of blood of these animals at regular intervals and their relations to each other studied:

1. Erythrocyte counts, leucocyte counts and hemoglobin determinations were made as previously described (1).

2. Hematocrit readings were made by centrifugating blood at a high constant rate of speed for five minutes.

3. Protein concentration of the blood was determined. For this a special technique was developed with the help of Dr. F. C. Koch of the University of Chicago whereby it was possible to make quantitative nitrogen determinations on a drop of blood secured from a needle prick of a vein of the guinea pig's ear. Thus the animal suffers from neither trauma nor undue loss of blood.

The blood was drawn into the Sahli hemoglobinometer pipette twice and ejected into a Hoskin's centrifuge tube containing 1 cc. of physiological salt solution with potassium oxalate (20 mgm. potassium oxalate to 100 cc. of the salt solution). This was centrifugated and 1 cc. of the diluted serum removed with a pipette and the nitrogen content determined by the Nessler-Winkler modification of the micro-Kjeldahl method as described by Folin and Farmer (6), except that a standard ammonium-sulphate solution of 0.25 mgm. of the nitrogen per 5 cc. of solution was used instead of one gram of nitrogen per 5 cc. of solution. The figures thus obtained represent the amount of serum nitrogen present in 40 cmm. of whole blood. To find the percentage of nitrogen in the serum the figures must be corrected with the hematocrit reading. This is the greatest source of error in the determination. But even this error is much less than that of an erythrocyte count, which has been estimated by Kjerpetersen (7) to be not less than 8 per cent.

Thirty guinea pigs were inoculated for this work in the hope that they would develop typical chronic tuberculosis. But of this group only five survived long enough for any very extensive study. An epidemic of acute infections and other causes carried off the others and the surviving five all proved to have acute tuberculosis. These were examined over a period of from three to five months. Three other old chronic tuberculous guinea pigs were also examined. These animals had lived nearly three years after inoculation. Tuberculin tests made by Dr. Esmond R. Long were negative, but autopsies revealed numerous small, very fibrous tubercles in the livers or spleens. The blood pictures were not altogether typical of our previous cases of chronic tuberculosis. Six normal animals were examined for six months.

We were therefore disappointed in the material available for our studies; nevertheless a few points of interest have been revealed by the results obtained.

By studying the relations between the hematocrit readings and the erythrocyte counts it was possible to determine the average erythrocyte volume and to follow their variations throughout the course of the acute tuberculosis that developed in our five guinea pigs. Considerable interest has lately been displayed in the study of cell volume. Capps (8) in 1903 called attention to the fact that the volume index of erythrocytes is of greater value in differentiating the anemias than the color index. He found that the volume of the cells varied directly with their hemoglobin content. The cells are never oversaturated, though he thought that in some conditions they might be less than saturated. This important point was apparently forgotten until the last year or two. Kammer, *et al.* (9), studied the cell volume in severe tuberculosis. They quoted Naegli as having determined the normal erythrocyte volume at $87\mu^3$ and Reich estimated it to be $92.2\mu^3$. Kammer *et al.* found it frequently reduced to $45\mu^3$ or $50\mu^3$ in tuberculosis. These figures occurred in cases where the erythrocyte count itself was not less than 4,000,000 and the hemoglobin percentage in many cases not less than 70 per cent. This brings out a point which will be discussed more fully later, namely, that the anemia in tuberculosis is undoubtedly much more severe than the routine blood examination would lead the examiner to suspect. Thus, in these instances the volume of the erythrocytes has been reduced to one-half and the color index is less than one; nevertheless the hemoglobin percentage has been reduced only one-fourth. The reason for this discrepancy is possibly an increased concentration of the blood. Campbell (10) reiterates the point that there is little change in the concentration of the hemoglobin in the corpuscle in various pathological conditions, but that the cell volume is increased about 30 per cent in pernicious anemia and decreased about the same amount in chlorosis and secondary anemias. Gram and Norgaard (11) state that the relation between hemoglobin percentage and cell volume is so constant in normal individuals as not to vary beyond the range of 2.22 to 2.46. Haden (12) emphasizes the value of these facts in differentiating the anemias.

In our work the erythrocyte volume was determined by dividing the hematocrit reading of the cellular mass by the erythrocyte count. An average result of forty-three examinations in six normal guinea pigs was $78\mu^3$ with a range of $70\mu^3$ to $87\mu^3$. Chart 1 shows the blood curve of a normal animal with an average erythrocyte volume of $78\mu^3$. But in the five cases of acute tuberculosis the cell volume decreased

rapidly. Thus in guinea pig no. 110 (see chart 2) the volume decreased from 84μ^3 to 62μ^3 in three months while the hemoglobin percentage decreased from 80 per cent to 70 per cent and the erythrocyte count increased. The color index dropped from 0.8 to 0.7. Thus the cellular volume decreased 25 per cent while the hemoglobin percentage and color index decreased by only 12 per cent.

Guinea pig no. 149 may be taken as another example (chart 3). Cellular volume decreased from 80μ^3 to 58μ^3 or 28 per cent in two months.

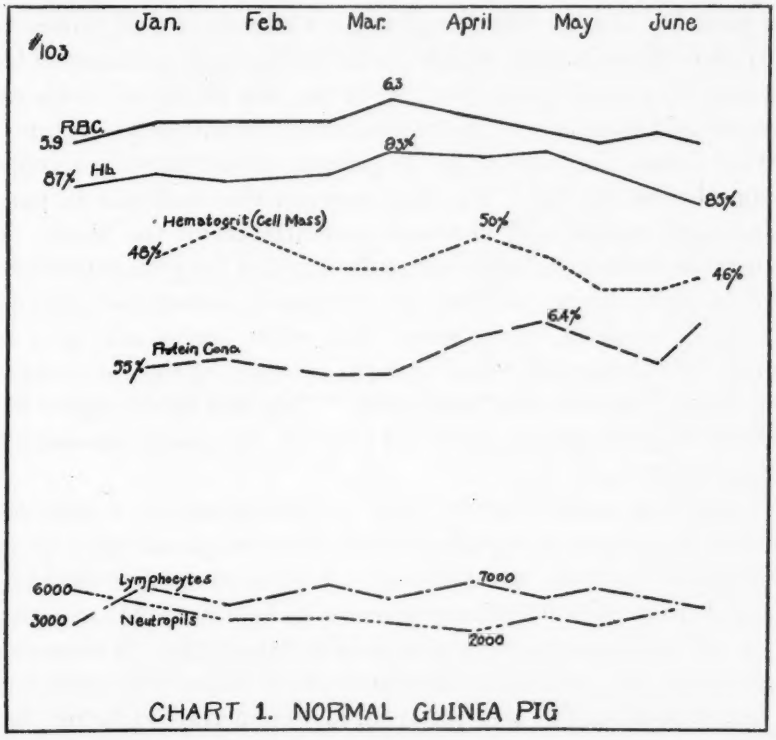

CHART 1. NORMAL GUINEA PIG

Hemoglobin percentage dropped from 76 per cent to 64 per cent, or 16 per cent. The other three animals showed similar conditions.

If now we study the protein concentration of the serum we find some explanation for the discrepancy. The average protein concentration for our normal animals was 5.9 per cent with a range of 4.4 per cent to 7.9 per cent. The average protein concentration of the five guinea pigs with acute tuberculosis was 6.6 per cent with a range of 5.2 per cent to 8.7 per cent. Thus in guinea pig no. 110 the average protein concentra-

tion was 6.6 per cent and in no. 149 it was 6.4 per cent. This represents an increase above normal of 9 per cent to 10 per cent which practically accounts for the difference of volume decrease of 25 per cent and hemoglobin percentage decrease of but 12 per cent, if we assume that the increase of protein concentration is due to dehydration or decreased blood volume.

From these facts it would appear that the routine blood examinations, including the cellular counts and hemoglobin percentage, are entirely inadequate to determine the grade and nature of the anemia in tuberculosis and probably also in other conditions. Cell-volume and protein-concentration determinations, which can be readily made on a drop of blood obtained by a needle-point puncture of the lobe of the ear in the usual way, will add materially to the information of the patient's condition.

What causes the increase in the protein concentration is a problem of considerable interest. We have assumed that it is due in part to a decreased volume and increased concentration of the blood. This assumption seems to be borne out by the fact that the percentage increase helps to fill in the gap between the decrease in hemoglobin percentage and the decrease in cell volume. Two other suggestions have been offered. Gullbring (13) found that the viscosity of the blood tends to vary directly with the leucocyte count. This idea would appear to be confirmed by us in guinea pig no. 144 (chart 4), but exactly the opposite is true in no. 109 (chart 5).

There is also an idea that the blood proteins increase as a result of the tissue destruction in the advanced tuberculous lesions and again decrease when severe cachexia is established. Figures to confirm this idea are offered from cases of pulmonary tuberculosis by Frisch (14) and Meyer-Bisch (15) and from tuberculous children by Mensi (16). It is impossible to show any such relation in the charts of our tuberculous guinea pigs. In fact it is difficult to account at all for the marked variations in the protein concentration of the blood in these cases of acute tuberculosis. All that can be said is that, on an average, the protein concentration is uniformly higher in acute tuberculosis than in the normal animals.

The question of dehydration or variation in blood volume and concentration is the one that originally interested us in this work and in our previous work with chronic tuberculosis. Unfortunately, it has been impossible for us to make direct blood-volume determinations. But even when these have been made on human subjects, the results have so far not agreed sufficiently to draw satisfactory conclusions.

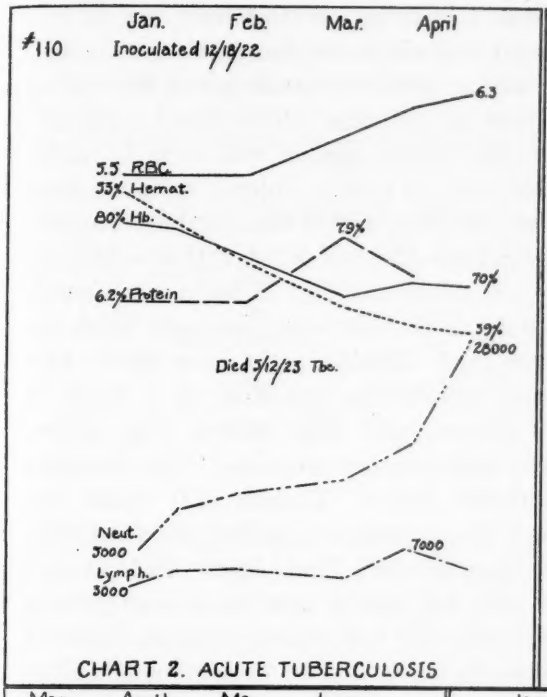

CHART 2. ACUTE TUBERCULOSIS

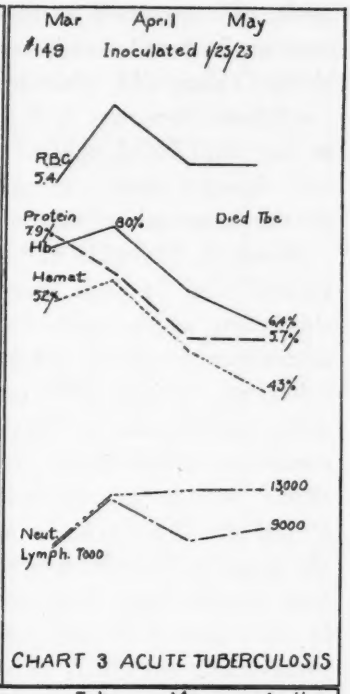

CHART 3 ACUTE TUBERCULOSIS

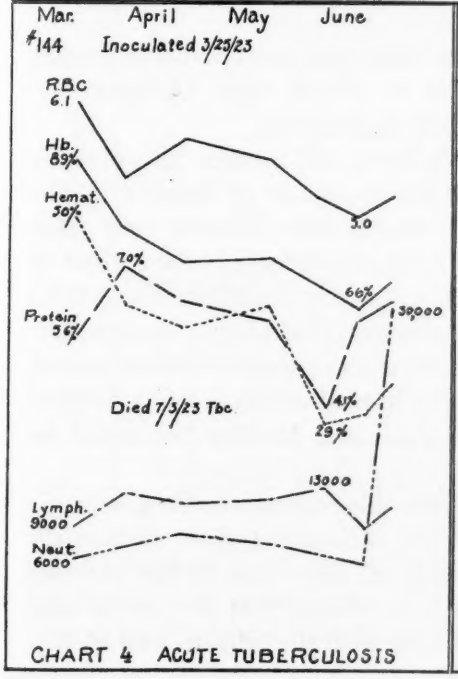

CHART 4 ACUTE TUBERCULOSIS

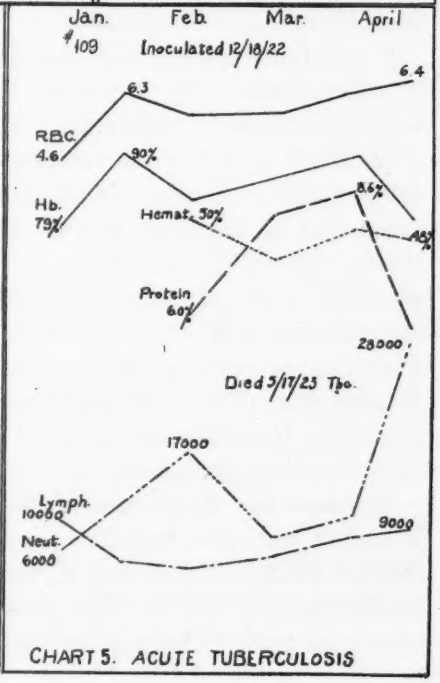

CHART 5. ACUTE TUBERCULOSIS

Boch (17) reports that plasma volume in terms of body weight was constant in health and in twenty-five widely varying pathological conditions. Denny (18) claimed that in pernicious anemia and some other conditions there was a decrease in cell mass which caused a decrease in the total blood volume as the plasma content was normal. Keith (19) thought there was an increase in plasma volume to compensate for the decrease in cellular mass, thus keeping the blood volume constant.

However, Underhill and Kapsinow (20) and Keith (21) have demonstrated that in dogs there is a steady decrease in blood volume with starvation which again returns to normal when food and drink are administered. Dale, Laidlaw, and Richards (22) have shown that injections of histamine cause a shock-like condition as a result of decreased circulating blood volume, and they believe that similar conditions might result from inflammatory processes. The histamine seems to act as an endothelial poison. Cannon (23) found that a fall in blood volume and blood pressure resulted from allowing the blood to flow through a region in which tissue injury had resulted from traumatism. Lansom (24) has shown that the sudden increase in the number of red blood cells per unit volume of blood, following intravenous injections of epinephrin, is due to passage of the blood fluids into the liver lymphatics.

It is certainly not inconceivable that some such process may be present in tuberculosis. The increased flow of lymph, after Gaertner and Roemer had injected tuberculin, further suggests this.

An effort to follow the relation between the protein concentration and the cellular elements in tuberculosis was made by Erben (25) who found that in the three patients he studied they followed each other closely. Bisch (26) showed an increased concentration of the blood in advanced cases of tuberculosis by examining the albumen and NaCl concentration of the serum and the hemoglobin percentage. At first there was an increased concentration which previous to death fell below normal. Atchley, *et al.* (27), made blood protein determinations in many diseased conditions including two cases of tuberculous pleurisy but found no deviations from the normal.

Although the three cases of chronic tuberculosis of the guinea pig which we were able to follow were not altogether typical, in that the cellular variations were not as marked as they were in our previous studies, such as they are they show quite clearly that the protein concentration tends to increase and decrease with the cellular, hemoglobin,

and hematocrit variations (chart 6). This suggests that a very important phenomenon in chronic tuberculosis is the change in the water content of the circulating blood. Such a condition must obviously lead to

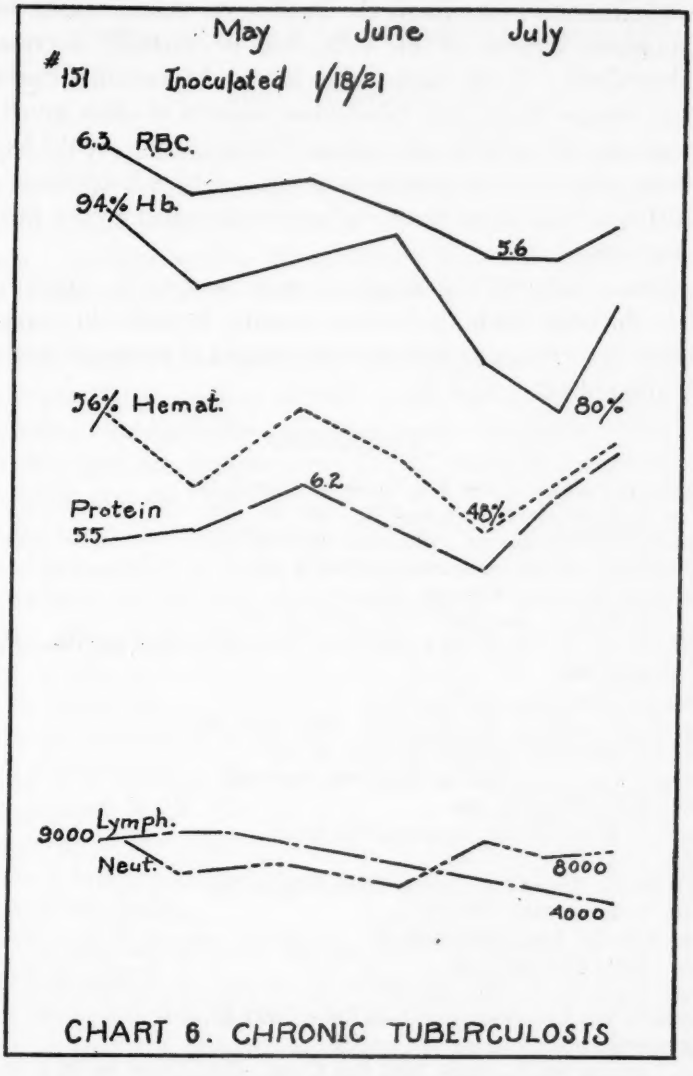

CHART 6. CHRONIC TUBERCULOSIS

much confusion as to the real condition of the patient's blood when conclusions are drawn from isolated routine examinations consisting only of cell counts and hemoglobin percentage determination.

CONCLUSIONS

Clearly our evidence is not as overwhelming as it might be but it is at least suggestive of certain important points:

1. In experimental tuberculosis the erythrocyte volume varies directly with hemoglobin content of the cells, and is markedly decreased in acute tuberculosis. If the same thing is true in human tuberculosis, as we have reason to believe, tuberculous anemia is often much more severe than the hemoglobin percentage determination would lead the examiner to suspect, as the condition is masked by a heightened serum concentration or decreased blood volume as revealed by an increased protein percentage.

2. In chronic tuberculosis of guinea pigs the protein concentration appears to fluctuate with the cellular counts, hemoglobin percentage and hematocrit readings, indicating a fluctuation of the water content of the circulating blood.

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AN ATTEMPT TO DETERMINE THE PRESENCE OF VITAMINES A AND B IN TUBERCLE BACILLI[1]

RUBY L. CUNNINGHAM

The origin of vitamines is being extensively studied at present. Brewer's yeast apparently manufactures and concentrates within itself a considerable amount of vitamine B. Possibly certain bacteria do this also. Because of the characteristic high fat content of tubercle bacilli it seemed possible that we might find in them the fat-soluble vitamine A.

Tubercle bacilli, as a waste product in the commercial preparation of tuberculin, were obtained for this study from the Cutter Laboratory in Berkeley, in approximately two-pound quantities every month. The strains used are designated as *K5*, *K7* and *K8*, and were originally from human sources. At the time of the experiment they had been cultivated for at least fifteen, nine and seven years respectively.

In the preparation of tuberculin the bacilli are incubated for thirteen weeks at 37°C., on a medium containing Liebig's meat extract, peptone, glycerine, sodium chloride and sodium carbonate in tap water. At the end of this time the culture and container are sterilized in flowing steam for three hours. The bacilli are then separated from the culture medium by filtration and for these experiments no attempt was made to further free the bacilli from the culture medium.

The mass of bacilli was preserved in a closed glass vessel in a refrigerator at a few degrees above the freezing point. At frequent intervals small quantities were removed to a small refrigerator for convenience in feeding.

For the determination of the fat-soluble vitamine rats were fed as indicated in table 1.

Tubercle bacilli were given to both the control and the experimental animals so that the proportion of the nutrient elements for the two groups would be equally modified and toxic substances, if present, would affect the two groups similarly.

[1] From the University of California, Berkeley, California.

Preliminary experiments not here recorded showed 1.5 gm. of moist tubercle bacilli to be about the maximum amount which could be daily made use of by the rats.

The animals were kept in separate standard cages in a room where the temperature could be regulated. They were given basal diet and water *ad libitum*. Measured amounts of yeast and tubercle bacilli were stirred into the daily feedings. Scattered food and that left in the feeding dish was reused and well stirred with the day's portion, so as to avoid the danger of selective eating on the part of the rats.

TABLE 1

	EXPERIMENTAL ANIMALS	CONTROLS
Crisco	20 per cent	20 per cent
Corn starch	56 per cent	56 per cent
Casein	18 per cent	18 per cent
Agar	2 per cent	2 per cent
Salt mixture	4 per cent	4 per cent
Dried brewer's yeast	0.5 gm. daily	0.5 gm. daily
Codliver oil		5 drops daily
Tubercle bacilli	1.5 gm. daily	1.5 gm. daily

TABLE 2

	EXPERIMENTAL ANIMALS	CONTROLS
Butter	10 per cent	10 per cent
Crisco	10 per cent	10 per cent
Corn starch	56 per cent	56 per cent
Casein	18 per cent	18 per cent
Agar	2 per cent	2 per cent
Salt mixture	4 per cent	4 per cent
Dried brewer's yeast		0.5 gm. daily
Codliver oil	3 to 7 drops daily	3 to 7 drops daily
Tubercle bacilli	1.5 gm. daily	1.5 gm. daily

The rats depending on tubercle bacilli as their only possible source of vitamine A began to fail in about one month. They then remained about stationary in weight, had a rough coat of fur and developed typical eye changes by the end of six weeks. Codliver oil was then added daily to their food and they grew rapidly, the fur became normal and the eye changes unless already destructive cleared up (chart 1).

For the determination of the vitamine B content of the tubercle bacillus the following diet was used (table 2) and under the same general condition as in the preceding experiment.

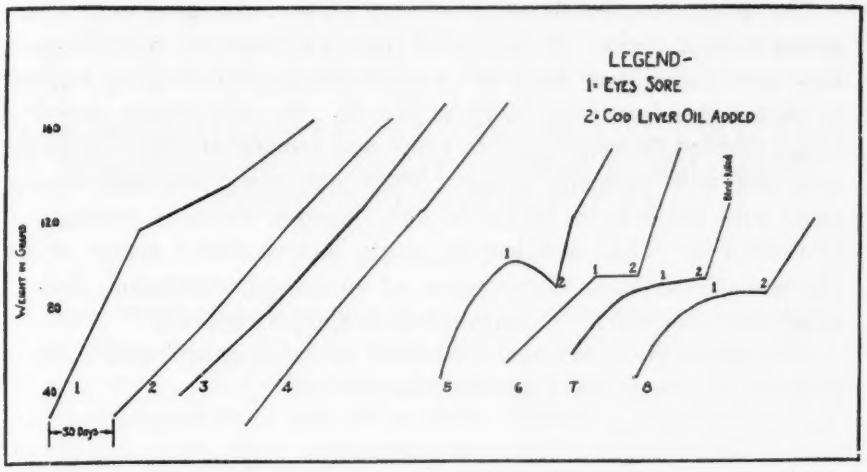

CHART 1. GROWTH CURVES OF ANIMALS OF VITAMINE-A EXPERIMENT

The control rats, 1, 2, 3 and 4, had satisfactory increases in weight with codliver oil as the source of vitamine A.

Rats 5, 6, 7 and 8 showed unsatisfactory growth curves, with a period of stationary or declining weight, when tubercle bacilli were given as the possible source of vitamine A. This was followed by a satisfactory growth curve when codliver oil was given daily.

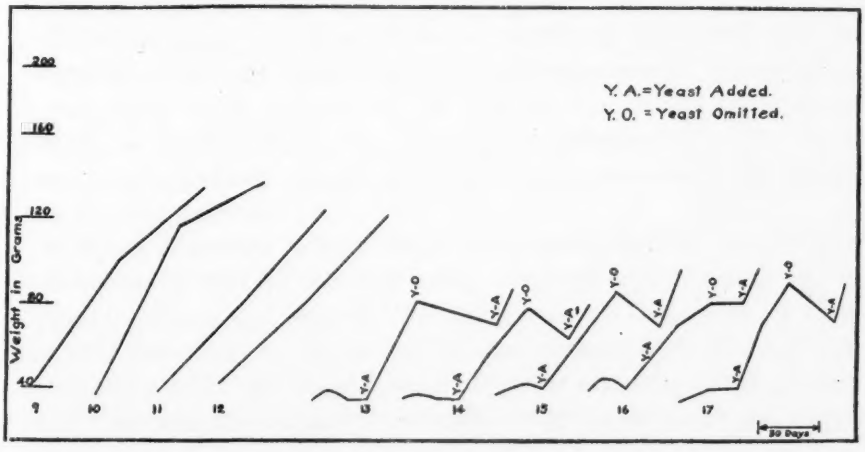

CHART 2. GROWTH CURVES OF ANIMALS OF VITAMINE-B EXPERIMENT

The control rats, 9, 10, 11 and 12, had satisfactory increases in weight with brewer's yeast for vitamine B.

Rats 13, 14, 15, 16 and 17 failed to grow when given tubercle bacilli as the only possible source of vitamine B. When brewer's yeast was added their growth was resumed.

The experimental animals grew very slowly, changing only a few grams in three weeks. At the end of that time yeast was added because they were eating very little and were physically deteriorating rapidly, so that it was feared that they might die. By three weeks they had about doubled in weight and in every way seemed normal. They ate well and were normally active. Yeast was again withheld, leaving them with tubercle bacilli as the only possible source of vitamine B in their diet. They now lost in weight and showed a return of the physical deterioration characteristic of vitamine-B starvation, that is, rough coat, slow stiff uncertain movements and poor appetite.

Addition of yeast was again attended by rapid growth and a return to an apparently normal condition (chart 2).

CONCLUSIONS

Tubercle bacilli known as strains *K5*, *K7* and *K8*, Cutter Laboratory, Berkeley, after being heated in flowing steam for three hours do not contain the fat-soluble vitamine which prevents the development of xerophthalmia, nor do they contain vitamine B.

THE PHYSIOLOGY OF THE ENDOTHELIAL CELL, ESPECIALLY ITS PERMEABILITY, UNDER NORMAL AND PATHOLOGICAL CONDITIONS[1]

R. S. CUNNINGHAM[2]

Since endothelium is present in all the blood vessels as a continuous lining membrane it is quite obvious that its importance in the body must be very great. But at the same time one must realize that the reactions and functions of these cells are entirely different in a layer such as the lining of a large artery than they are in the wall of a capillary. The physiological importance of the endothelial lining of large arteries and veins consists in its efficiency as a smooth lining, the surface of which does not easily impede the passage of the blood-stream and which offers no irregularities to which cells or masses of cells can adhere. The physiology of endothelium as a tissue, or of the endothelial cells as separate structures, does not become in any sense apparent until one turns to the study of the smaller radicles of the vascular system, the capillaries. This is obvious because it is only in the capillary that one can study the endothelium alone, and where it is not intimately connected with the muscular and adventitial layers as it is in the larger vessels. Furthermore, the capillary is the segment of the vascular tree where the greatest activity is located, where the exchange of substances for the use of tissue cells takes place and where excretory substances make their escape into the blood-stream.

It will be important to note that in this communication I use the term *endothelium* to refer to the cells lining the blood-vascular and lymph-vascular systems and exclude the lining cells of the serous cavities. The cells lining the pleural, pericardial, and peritoneal cavities are commonly included in the designation *endothelium* and have many characteristic reactions in common with the cells lining blood vessels and lymph

[1] Presented at a symposium on "The Endothelial Cell," arranged by the Medical Research Committee, before the Pathological Section of the twentieth annual meeting of the National Tuberculosis Association, Atlanta, Georgia, May 9, 1924.

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vessels; therefore, I will discuss their reactions to some extent, but it seems advisable to distinctly separate the two groups of cells and consequently I have adopted the term *mesothelium* for the lining cells of the serous cavities.

Endothelium as a cellular membrane was first differentiated by Von Recklinghausen, who found that by means of the silver-nitrate reaction the intercellular lines were made sharply apparent by the application of this salt and subsequent reduction with sunlight. From the time of this discovery to the present there has been wide discussion regarding the possibility of openings of various kinds being present between the endothelial cells, and those workers who have championed the presence of these openings have based their conclusions upon the histological pictures presented in silver-nitrate preparations. The nature of the silver-nitrate lines, whether intracellular concentrations of electrolytes or an intercellular cement substance, has been discussed fully by A. B. Macallum and need not be referred to further at this time. The importance for us, however, lies in the bearing which these openings between or surrounded by the endothelial cells might have upon the question of permeability. The structure of the capillary wall has been thoroughly discussed by Professor William Snow Miller and, in consequence, need not be referred to here in detail; it will, however, be necessary to refer from time to time quite briefly to those points in the structure of the capillaries and lymphatics that are essential to the discussion at the moment.

I expect to discuss the physiology of endothelium under three general heads: (1) the independent contractility of the capillary endothelium; (2) the permeability of endothelium; and (3) the rôle of endothelium as an *anlage* for phagocytic mononuclear cells.

1. THE INDEPENDENT CONTRACTILITY OF THE CAPILLARY ENDOTHELIUM

The contractile element and its nerve supply: The basis for our present conceptions of the contractility of capillaries depends largely upon the observations of Krogh, Vimtrup, and Clark and Clark. But while these observers have done much to advance our knowledge of the subject during the last few years, there are numerous observations of great interest which have preceded them. The first observation which bears upon the ability of the capillaries to actively change their size was that of Lister (1858), who observed a definite dilatation of the capillaries during inflammation, but he concluded that this reaction was passive, being brought about

by pressure from the arteries. To Stricker (1865) must be credited the first direct observations of independent contractility of the endothelial wall. These findings were questioned by numerous observers, but were confirmed by Roy and Brown (1879), who went further and measured the pressure in the capillaries, and by Steinach and Kahn (1903). There has been a great deal of work by a large number of observers among whom were Ebbecke; Cotton, Slade and Lewis; Dale and Richards; Hooker and others; all of which has been important in establishing much of the normal physiology of the *flow of blood through the capillaries*. But, while these observations are of the utmost importance for the physiology of the circulation, they contribute but little to the physiology of endothelium beyond establishing the exact amount of the available hydrostatic pressure in the capillaries. All of these observations have assisted in establishing the fact of the independent contractility of the capillary, but none of them has given any specific evidence bearing upon the mechanism as it involved the individual endothelial cell.

Rouget (1873) described the independent contractility of endothelium but referred the mechanism, not to the endothelial cells, but to certain large elements which he observed attached to the wall of the capillaries, and which he assumed were related to the smooth muscle cells of larger vessels. These cells were rediscovered by Meyer (1902) and were recently studied in detail by Vimtrup. Vimtrup, Rehberg, and Krogh, have all concluded that these cells represent the active contractile elements of the capillary and that the nerve endings are upon them and not upon the endothelial cells themselves. Recently Clark and Clark have studied capillaries in the tadpole's tail, and have demonstrated that the endothelium is capable of contracting even before the Rouget cells appear, and that in many capillaries where the Rouget cells are widely separated it can be seen that there are many more contractions initiated in those areas where there do not appear to be any Rouget cells than in those which are directly under them. Thus it seems unquestionably demonstrated that the capillaries have a distinct power of contractility, and, while there is some question as to whether the contractile element is the Rouget cell or the endothelial cell, or both, the most recent studies on the living animal indicate that, at least in some cases, the endothelial cell is truly a contractile element. It will not be necessary to go into the question of the nerve supply of endothelium further than to state that, if Clark and Clark are correct in concluding that the contraction of capil-

laries is due to the direct action of the endothelium, then all of the observations of Beale, Glaser, Krimke, Hofman, and Krogh are concerned with the response of endothelium and not that of muscles or adventitial cells to nervous stimuli. It will be sufficient to note here that the contractile element very probably receives both constrictor and dilator fibres and that, as in the case of the other blood vessels, the first come by way of ventral roots while the latter are dorsal root fibres. For further information on this very important and interesting subject the recent reviews by Krogh and Ebbecke are recommended.

Hormonal control of the capillaries: Krogh found that when he perfused the hind limbs of a frog with Ringer's solution the capillaries dilated in a very few minutes and remained in a state of complete relaxation. If, on the other hand, ox blood was added to the perfusion fluid the capillaries maintained their tonus for from 40 minutes to 2 hours. Krogh next found that he could dialyze the substance which was accountable for the maintenance of capillary tonus out of the blood of the ox by long continued exposure to Ringer's solution, and he called this substance the *X-substance.* Krogh and Rehberg next found that removal of the hypophysis caused a great dilatation of the capillaries of the muscle of the frog's foot, and then by further experiments they found that injections of pituitrine extract caused a very profound contraction of the capillaries. They also concluded that the so called X-substance was identical with the pituitrine or extract of the nervous and intermediate parts of the hypophysis. Thus it seems certain that there is a substance, probably produced by the hypophysis, which is circulating in the blood-stream in a concentration somewhere between 1/10,000 and 1/1,000,000 the strength of the Parke, Davis pituitrine extract and which is intimately concerned in the maintenance of the tone of the capillary wall. This work is still very inconclusive, and much more will have to be carried out before we will have any satisfactory conception of the physiology of the capillaries from the standpoint of their vasomotor reactions and their nervous and hormonal control.

Reactions of the capillaries to physical stimuli and to various capillary poisons: A great many investigations have been carried out with regard to the reactions of capillaries to external stimuli, and these have been divided by Krogh into two groups: those that act directly upon the contractile element and those that act indirectly, that is, through changes in the environment or upon the nerves or nerve endings.

Physical stimuli: Natus, Ricker and Regendanz, Brund and König, and Carrier have investigated the effects of heat and cold upon the capil-

laries, and have shown that in general the dilatation produced by heat is in part a reflex and in part a direct action on the capillaries themselves, and that the initial contraction due to cold is similarly a mixed reaction. But they conclude that the prolonged and extreme dilatation that comes on with long exposure to intense cold is certainly due to a paralysis of the contractile element. Niels Finsen and his students have studied the effects of chemically active light rays, and have found that the capillaries were dilated as the result of a direct action on the contractile elements.

Chemical stimuli: The importance of the action of chemical stimuli on the capillary is due to the rôle which some of these known substances, and probably many others as yet undiscovered, play in inflammation and in shock. Such foreign substances as iodine, abrine, mustard oil, acetyl-cholin, and certain double salts of the heavy metals have been found to be definite capillary poisons. Some of these substances may, on occasion, cause constriction when in very dilute solution but, in general, they all have the same effect, that is, the production of extreme dilatation. Even more important is the reaction of the capillaries toward histamine, a substance obtained from the decomposition of tissues. The effect of this substance has been studied by Dale and Laidlaw, Abel, Rich, Doan and Krogh. The action of histamine on the endothelium is quite similar to that of the other capillary poisons mentioned above, but its importance lies in the fact that it, and numerous allied substances, are formed in the tissues themselves. At any rate, it is important to note that all capillary poisons produce dilatations, and hence tend to bring about the opposite state from that produced by the activity of the hormone described by Krogh. It would be very important if it could be demonstrated that there is a balance of capillary activity maintained by means of tissue products on the one hand and a specific hormone, the X-substance of Krogh, on the other. Finally, there is some evidence that the oxygen-carbon dioxide ratio is of importance for the maintenance of normal capillary activity, but the direct effect is probably small in contrast with that played by the hormone described above. A decrease in the amount of oxygen will cause the opening up of collapsed capillaries; but it is not clear whether this is direct or due to the coincident increase in H-ion concentration. It has been shown that an increased H-ion concentration results in the dilatation of all the vessels, and especially the arteries.

2. THE PERMEABILITY OF ENDOTHELIUM

Introduction: When we consider the fact that all the substances which are utilized by the cells of the body, and all the waste products coming from them, must pass through the endothelial wall of the capillaries, we realize the immense importance which the problems of endothelial permeability have for the physiologist. We will first consider the status of our information concerning the endothelium lining the general vascular tree and the lymphatic capillaries, and then examine the special peculiarities of the endothelium of spleen, liver, lymph nodes, and bone marrow.

Physical openings through the endothelium: stigmata, stomata, and physiological separations: The earlier conception of histologists that there were true physical openings in the walls of capillaries, through which there was an active interchange of substances between the blood and tissue spaces, was largely dependent for evidence upon Von Recklinghausen's experiments with silver nitrate. The "openings" which he designated as *stigmata* and *stomata* were very generally accepted until MacCallum's work on the diaphragm in 1903, since when they have survived only in textbooks and in the case of a few isolated investigations. MacCallum however suggests in his conclusions that, during absorption of substances from the peritoneal cavity into the lymphatic lacunae of the diaphragm, these substances pass both through and between the cells of the mesothelial layer and those of the lymphatic endothelium. It has also been widely accepted in the literature that a similar state of things exists in the capillaries, and that, under certain physiological or pathological states, openings are formed in the so called intercellular cement through which substances pass in both directions. Thus the stigmata and stomata gave way to a conception of much finer openings which were produced by changes in the physiological state of the endothelial cell.

A great deal of recent work indicates very strongly that the mechanism of physical openings outlined above is not the correct explanation of the way in which substances pass the endothelial membrane; but that all such interchange, even of particulate matter, takes place directly through the cytoplasm of the cells. The most important of these observations are undoubtedly those of Krogh. In the course of his studies on the effects of dilatation and constriction of the capillaries, he noticed that, when a capillary was dilated widely, as, for instance, after the

application of urethane, the plasma gradually disappeared and left the dilated vessel packed with red blood-cells. It was obvious that when the vessel had dilated some change had taken place in its wall, allowing the escape of all the constituents, including the serum proteins, into the surrounding tissues, and this indicated both that the endothelium had become much more permeable than normal,[3] and that the limit of this permeability was greater than the size of the serum-protein molecules. Because of this suggestive result Krogh carried out some experiments to determine the limits of size of the particles to which the normal and dilated capillary walls were permeable. He states that his experiments were not entirely successful for this purpose; but it seems to me that they are, nevertheless, of great significance with regard to the route followed by substances escaping through the capillary wall. He studied brilliant vital red and Chicago blue 6 B, and found that they diffused slowly through the normal capillary wall of the frog's tongue, but that when the capillaries were moderately dilated they were closely surrounded by a stained zone. He also tried soluble starch, the particles of which are about 5 micra micra in diameter, and these proved to be entirely held back by the normal, but passed through a strongly dilated capillary. By careful preparation he was able to obtain a suspension of India ink in which the particles were about 200 micra micra. When this was injected into the circulation he found that even with the maximal dilatation the ink was quantitatively retained. It is obvious that both these experiments indicate that there is no separation of the endothelium because, if such had been the case, at some place or other there would have been "holes" large enough for some ink to pass; and in the vital-red experiment the line of color external to the endothelium would have been irregular, had it escaped through separate holes in the endothelial wall. These experiments show very definitely that the permeability of endothelium is a factor of the cytoplasm itself and not dependent upon separation of the cells.

Turning now to the lining cells of the peritoneum and the lymphatics of the diaphragm, my own work has indicated that a similar conclusion can be reached in regard to them. I have studied the absorption of

[3] I use the term "normal" condition of the capillary to refer to that state of tonus when the capillary is neither constricted so that the circulation is impeded nor dilated so that stasis can begin to develop. For further discussion of the various stages between extreme constriction and extreme dilatation see Krogh's monograph on the capillary.

both solutions and particulate matter from the peritoneal cavity, and in every case all were found to pass through the cytoplasm of the cells. With particulate matter the principal route is through the diaphragmatic lymphatics, and I have found that the mechanism in this case is principally the mechanical forcing of the particles into the cytoplasm of the mesothelial cells and their subsequent discharge into the lymphatic lacunae or tissue spaces. That the pumping action of the diaphragm is the force which brings about this passage was shown by the series of experiments on fetuses before and after they had begun spasmodic breathing movements. We are here obviously dealing with a mechanism wholly different from that involved in the passage of solutions and the finer submicroscopic particles (for instance, vital dyes), and in all probability it is allied with the usual phagocytic action of cells. Further observations on the peritoneum have given some additional evidence for the intracellular route followed by diffusible substances. Shipley and I studied the absorption of iron ammonium citrate and sodium ferrocyanide through the omentum, by withdrawing that structure through an incision and immersing it in a solution of the salts. We found that both salts diffused directly into the blood vessels of the omentum; and when the omentum was fixed in an acid medium, and sections prepared, Prussian-blue granules were found in the cytoplasm of the endothelial cells through which the salts had obviously passed. Finally I found that in experimentally produced, hydremic plethora there was a great transudation of fluid through the spleen into the peritoneal cavity; and that, during this passage, each mesothelial cell on the spleen became markedly edematous. This occurred when solutions of foreign salts were introduced into the blood-stream as well as with physiological saline, Ringer's solution, etc. When sodium ferrocyanide and iron ammonium citrate were used, Prussian blue could be precipitated in these vacuolated cells. These findings seem to me to be satisfactory evidence that the passage of fluids and salts into the peritoneum takes place through the cells and not between them, as has been so often claimed.

Taking all of this evidence together it seems then to be conclusively proved that the permeability of endothelium and mesothelium is a factor of the cytoplasm itself.

Differential permeability of endothelium: Having determined the fact that the passage of substances takes place through and not between the endothelial cells, it is important to point out that there is a wide varia-

tion in the degree of permeability of different groups of capillaries. Starling found that lymph coming from the liver contained more protein than that from the intestines, which in turn contained more than that obtained from the limbs, where the percentage was very low. This was the first definite demonstration of a difference in the permeability of different groups of capillaries. Following this discovery, Starling demonstrated that when one of the legs of a dog was made edematous by the injection of 1 per cent sodium-chloride solution and both were perfused with defibrinated blood, the blood from the normal limb remained unaltered while that from the edematous side became more dilute. He explained this absorption of extravascular fluid on the basis of the constant osmotic pressure exerted by the colloids in the blood, which could not diffuse into the edematous tissue spaces. This pressure has been variously estimated at from 30 to 60 mm. of mercury, and it has been shown further that there is wide variation in the pressure in different animals. It seems, therefore, that the capillaries of the legs have a permeability such that most of the proteins are retained while the majority of crystalloids pass with comparative ease, while those of the liver allow the proteins also to pass almost, if not wholly, quantitatively. In the case of the spleen there is a very special arrangement of the endothelium which allows the passage of formed elements. This peculiar perforated endothelium was described by Mall and by Mollier. The cells lining the arterial ampullae and the venous sinuses are very large and have a cytoplasm filled with a definite fretwork of spaces, each large enough to permit the passage of red blood-cells. As far as has been determined there is no other place where this peculiar type of endothelium exists and where there is, in consequence, an entirely open circulation. The lymphatic endothelium is in general much more permeable than that of the blood vessels; this is shown by the absorption of fat in the intestinal villi, and by the ease with which particulate matter obtains entrance to lymphatics. It has also been shown by Lewis, and others, that colloids are absorbed much more rapidly by lymphatics than by capillaries. However, it is important to note here that no studies have been made upon lymphatics which are in any way comparable to those of Krogh and his collaborators on the blood-vascular capillaries.

The secretory activity of endothelium: There has been a very intense controversy as to whether endothelium always acts as a simple membrane, capable of variable permeability, or whether it participates actively

in the formation of lymph, and in the various secretory activities of the organs. Heidenhain has been the chief exponent of the latter hypothesis and has adduced as evidence the fact that often the lymph of the thoracic duct contains a higher percentage of a given substance, whether a normal constituent or experimentally exhibited, than the blood-stream. He also pointed out that there are many places in the body where substances are taken from the blood and transferred to a given secretion in such quantities that the process cannot be explained by osmosis and diffusion. The much higher percentage of calcium in milk than in blood is an example of this type of activity. Heidenhain thought that the endothelium was responsible for at least a part of the work done in this transfer of calcium, but it is also possible to explain it in another way. If, as has been pointed out by many observers, the endothelium is permeable to the substance in question, in this case calcium, there need only be postulated a special activity on the part of the gland-cell, which, by constantly removing the calcium that had diffused out of the blood creates a low pressure area into which more calcium can diffuse. Thus, these observers consider the endothelium to be inert so far as assisting the secretory act is concerned. Whether or not the endothelial cell plays an active rôle in the formation of lymph is still disputed, but Krogh voices the opinion held by the majority of observers that endothelium does not participate in the activity which is commonly known as secretion.

Changes in the permeability of endothelium; theories of the mechanism involved; and the importance of these changes in disease processes, especially edema: It is now established quite definitely that endothelium is everywhere permeable to gases and that their passage is controlled exclusively by osmosis and diffusion. Endothelium seems also to be generally permeable to the crystalloids, though here, as we have seen above, there is some argument with regard to the mechanism involved in their passage through the cells (Heidenhain, Volhard, etc.). But the weight of evidence is that crystalloids, at least for the most part, pass the endothelial membrane by diffusion. Schulemann has studied the diffusion of a large series of dyes from the subcutaneous tissues of mice, and found that they were distributed throughout the body by diffusion, at rates which paralleled their rates of diffusion through gelatin. Colloids on the other hand, as was described above, do not generally pass through the capillary wall and hence are not absorbed from the subcutaneous tissues under normal circumstances. This corresponds exactly with Schulemann's observa-

tions that dyes, which would not diffuse from a watery solution into gelatin, remained localized when injected into animals and were only taken up by the neighboring cells. This semipermeability of the capillaries to colloids was also shown by some recent observations of Lewis (1921), who injected a serum which he was able to recognize by a complement-fixation reaction and found that he could detect it in the thoracic-duct lymph after 40 minutes, but that it did not appear in the blood in appreciable amount until after 3½ hours. Thus it seems clear that the normal peripheral capillaries are permeable to water, gases and crystalloids, but semipermeable toward substances of which the molecular or particulate size is as great or greater than that of the serum proteins. It is on the basis of these conclusions that Starling emphasizes the importance of the osmotic pressure of the colloids of the blood for the maintenance of blood-volume and the absorption of extravascular collections of fluid.

We come now to a consideration of the theories with regard to the mechanism involved in variations of permeability and the bearing that these may have upon edema. Krogh has concluded from his experiments that dilatation of the capillaries is the most important if not the sole factor in the regulation of its permeability; but his observations do not assist in explaining either what the actual change in the endothelial cell is, when it passes from a contracted to a relaxed state, or why the stretched cell is more permeable than the contracted one. However, it seems entirely certain that in some way the dilatation of the capillary and, hence, the stretching or thinning of the endothelium must increase its permeability and allow substances of larger particulate size to pass than is the case with normal endothelium.

Cohnheim and Lichtheim and Magnus found that animals could be given a large amount of physiological saline solution without the development of any subcutaneous edema, but they discovered that if this same animal was then subjected to the application of heat, iodine or other irritant, edema developed. They explained this as the result of injury to the endothelium, and this view has been widely accepted as the explanation of inflammatory edemas. It seems evident that irritants produce changes in the endothelial cells, but whether these changes are the results of relaxation, the cause of the relaxation, or merely concomitant with it is not as yet clear.

Hamburger and his collaborators have concluded from a series of elaborate experiments that the balance between the calcium and sodium ions

is the important factor in maintaining the normal state of the endothelium, and that changes in the ideal, balanced ratios of these two salts will bring on edema. While no observations have been made directly upon the mechanism of this reaction, Hamburger has pointed out that the experiments of Clowes on the effect of calcium on oil-water emulsions form a beautiful parallel in the inanimate field. On the other hand, Zwaardemaker and Gunzberg have concluded that the normal tonicity of the endothelium depends upon the presence of the radioactive potassium ions; and they contend that perfusion fluids without potassium allow the immediate development of edema while the addition of either potassium or some other radioactive element will prevent the appearance of edema.

There seems to be little doubt that increased permeability of the endothelium is one of the most important factors in the production of edema both of a local and general character. This seems to be especially true of the inflammatory edemas. But it is difficult, if not impossible, to come to any definite conclusions, at the present time, with regard to these various and antagonistic explanations of the mechanism involved.

The specific endothelia: It is necessary to point out here that there are certain vascular beds which are lined by special types of endothelial cells. These are the blood-sinuses of spleen, liver and bone-marrow, and the lymph-sinuses of lymph nodes. These endothelial cells have in common a considerable ability for phagocytizing foreign material but there is wide variation within the group; those lining the spleen and liver are the most active and those in the bone-marrow the least. The endothelium of the splenic sinuses and the arterial ampullae are peculiar also, in that they are perforated, as has been described above. There is some question as to whether the endothelium of the liver-sinuses is complete or not; and it is well known that there are very specialized endothelial cells, derived from the lining cells and usually closely attached to them, which are highly phagocytic. These are the so called Kupffer cells, and are, I think, identical with the clasmatocytes. The discussion of the part that these special endothelial cells take in the production of the phagocytic mononuclears will be discussed later.

Finally, the endothelium of the bone-marrow is distinctive, not only because of its phagocytic ability, but also because it retains the embryonic function of producing red blood-cells. The blood vessels of the bone-marrow are very characteristically arranged, as has been shown by Doan. He found that there were two types of capillaries, one set that connected the arterioles with the venous sinuses, and another

set, which he described for the first time, that connected sinus with sinus. These intersinusoidal capillaries are apparently seldom patent to the blood-cells, but usually remain closed, and only open up under special circumstances; their special function has been definitely shown to be the formation of young red blood-cells. Doan was able to demonstrate this in the pigeon by reducing the marrow to a very hypoplastic state by starvation and then feeding for various periods of time. In this way he was able to eliminate practically all the free cells of the marrow and to show that, on the resumption of feeding, the endothelium of these collapsed capillaries divided and formed, intravascularly, large numbers of megaloblasts. Doan and I have been able to show the same activity in the marrow of the rabbit by other methods; and we were further able to show that even the endothelium of the sinuses could, upon sufficient demand for increased erythrocytic production, proliferate and produce megaloblasts.

3. THE RÔLE OF ENDOTHELIUM AS AN ANLAGE FOR PHAGOCYTIC MONONUCLEAR CELLS

The observations of Mallory in 1898 on the phagocytic mononuclear cells found in the lymph nodes in typhoid fever established the concept of the endothelial derivation of these cells. He called them *endothelial leucocytes*. Permar, McJunkin, and Foot have extended the observations of Mallory to the lungs, omentum and general connective tissues, and they have uniformly supported Mallory's conclusion that the phagocytic mononuclears are everywhere derived from the endothelium of the smaller blood vessels by active proliferation. It will not be necessary to give any of the evidence for this conclusion as Dr. Permar will present that in his communication. Sabin, studying the membranes of the embyro chick, demonstrated that there were certain large phagocytic cells which were derived from the endothelium, on and after the third day of incubation, and these cells she identified as the clasmatocyte or histiocyte of the connective tissues. H. M. Evans and his collaborators have shown that the endothelium of the lymph nodes, spleen, liver and bone-marrow reacts very strongly to vital stains and they have concluded that these so called "specific endothelia" are the source of the clasmatocytes or histiocytes.

Aschoff and Kiyono have gone further and have included these special endothelial cells in their great class of *reticulo-endothelium* and they have referred the origin of the phagocytic mononuclears to this "tissue."

This concept of the reticulo-endothelial apparatus as a tissue of embryonic characteristics and combining in one group both the specific endothelia of the students of vital stains and the so called reticular cells, has become widely accepted, especially in Germany. Numerous workers have indeed begun to refer many of the blood-diseases to derangements of the reticulo-endothelial apparatus. Aschoff and Kiyono also identified the mononuclear cells of the blood-stream, which have been variously called *transitionals, large mononuclears or monocytes* with the great phagocytic cells of the tissues, the *clasmatocytes, histiocytes* or *macrophages*. It has thus become generally accepted that the monocytes of the blood-stream and the clasmatocytes of the connective tissues are identical and that they are derived from the reticulo-endothelial apparatus.

Certain observations which we[4] have been carrying out during the past year have caused us to reject the concept, outlined above, of the identity and common origin of all phagocytic mononuclears. We have studied the cells that can be obtained by puncture of the spleen of living animals with the supravital method and have been able to separate the phagocytic mononuclears very sharply into two distinct groups, and have also been able to adduce some very satisfactory evidence of the totally distinct origin of these two groups of cells. The method of supravital staining has already been of great value in the analysis of the types and characteristics of blood-cells in both experimental and clinical investigations and we hope that its use will be widely extended in the study of blood and tissue-cells. The method has been given in detail by Sabin in the *Johns Hopkins Hospital Bulletin*, 1923, xxxiv, 277-288. In applying the neutral red-Janus green technique to the splenic punctures we have found that the mononuclear cells can be divided into two distinct groups by means of the type and distribution of the neutral-red granules and vacuoles, the specific color which these present, the manner in which these cells store phagocytized material and in the number and characteristics of their mitochondria. The most specifically characteristic point is the fact that the monocyte has almost invariably a definite centrosphere, about which the neutral-red granules are arranged in a rosette, with the dye inclosures varying from very small aggrega-

[4] This work has been carried out by Dr. F. R. Sabin, Dr. C. A. Doan and myself, and part of it has been published in the *Proceedings of the Society for Experimental Biology and Medicine*, 1924, xxi, no. 6, pp. 326 and 330. Further reports on this subject including many of the observations mentioned will be published in the near future.

tions adjacent to the centrosphere to much larger ones in the periphery. It is in the region of these larger collections of neutral red that phagocytized cells or masses of debris are uniformly stored. In contrast to the reaction of the monocyte, the clasmatocyte or histiocyte of the spleen is a cell in which the neutral-red inclosures are distributed indiscriminately throughout the cell without any pattern whatever. The first material ingested by the clasmatocyte is invariably stored adjacent to the nucleus, and gradually the entire cytoplasm becomes filled with cells or debris. In addition, the clasmatocyte contains very few scattered mitochondria or none at all, while the monocyte usually contains many mitochondria which are specifically arranged about the rosette of neutral red and about the convex surface of the nucleus. We have further extended these observations to peritoneal exudates and subcutaneous irritations and have found both types of cells in these areas as well.

In another series of unpublished experiments I have been able to demonstrate that in the spleen there is a very sharp differentiation between the endothelial cells of the sinuses and the so called reticular cells of the pulp; and feel wholly justified in stating that, as far as the spleen is concerned, the endothelium and reticulum are entirely distinct and the term *reticulo-endothelium* meaningless. This separation has been arrived at by means of the fact that the endothelial cells are capable of phagocytizing much larger particles than the reticular cells and so, by using graded sizes of particles (vital stains, India ink, cinnabar and foreign erythrocytes), it has become wholly clear that there is no endothelial channel between the arterial end-bulbs of Thoma and the elaborate plexus of venous sinuses. In the spleen of a rabbit which has been injected repeatedly with India ink, in which most of the particles are very large, the entire endothelial lining of the sinuses can be seen loaded with carbon in very sharp contrast to the pulp cells which contain very few, fine ink particles. The circulation passes through the perforations in the endothelium of the bulbs into pulp spaces wholly devoid of endothelium, and from these spaces into the sinuses through similar perforated endothelial cells. This peculiar perforation of the endothelial cells of the spleen was shown by Mall and by Mollier but has been rather widely neglected. In my own experiments these perforations of the endothelium have been found to be quite characteristic of the endothelial cells of the spleen and there is no evidence whatever for considering them as artifacts. Furthermore, I have found that in most of these animals which had received intravenous injections of the substances

mentioned above the endothelium was proliferating actively and producing large phagocytic mononuclear cells, which either remained attached, as in the case of the Kupffer cell of the liver, or became free in the blood-stream, or wandered out into the pulp. But there was never any evidence that the less highly phagocytic reticulum was engaged in producing these cells, which I have identified as clasmatocytes or histiocytes.

Critically speaking, I now feel that we can accept as definitely established, from all the evidence given above, that the histiocyte or clasmatocyte is derived from the specific endothelium of liver, spleen, bone-marrow, and lymph nodes in the adult, and from the general endothelium in the embryo. And it seems also clear that the *endothelial leucocyte* of Mallory, the *histiocyte* of Aschoff and Kiyono, the *macrophage* of Evans, and the *clasmatocyte* described by Sabin in the embryo chick are identical and are true derivatives of the endothelium. It is still, it seems to me, an open question as to whether clasmatocytes are derived only from the endothelium of spleen, liver, lymph nodes and bone-marrow, or whether they may also be produced during irritations from the general vascular endothelium in the adult, as claimed by Permar and Foot. I have elsewhere published a statement that I have seen some evidence suggestive of the origin of clasmatocytes from the endothelium of blood vessels, the blood supply of which had been greatly reduced. So far I have been able neither to confirm nor disprove these observations and feel that it is still an open question. We have great hopes that further work on inflammatory reactions in the subcutaneous tissues with the supravital dyes may assist in definitely establishing whether the source of the numerous clasmatocytes found there is by active division of previously formed clasmatocytes or by the proliferation of the endothelium of adjacent blood-vessels. The latter explanation would be the more harmonious with our other conclusions but so far I do not feel that the work is entirely conclusive.

Turning now to the question of the origin of the monocyte, we have concluded, as the result of a large number of observations[5] on the developing cells obtained by puncture of spleen and bone-marrow, that the adult monocyte of the circulating blood is derived from a primitive stem-cell which in turn comes from the reticular or mesenchymal cell. This primitive stem-cell is also the parent stem from which the leucocytic and lymphocytic series of cells are derived.[5] We have also found that the monocyte retains its capability to reproduce by division in the spleen, bone-marrow and blood-stream, and in exudates obtained from irritated peritoneal and subcutaneous tissues.[5]

[5] See footnote 4.

THE FUNCTION OF THE ENDOTHELIAL CELL IN PATHOLOGICAL CONDITIONS, ESPECIALLY IN TUBERCULOSIS[1,2]

HOWARD H. PERMAR

Of late years numbers of carefully worked out experimental studies on diverse phases of the problem of the function of the endothelial cell in pathological states have appeared which have justified Mallory's (1) interpretation of the large mononuclear wandering cells of the tissues and circulating blood. We may mention only a few, such as the work of Haythorn (2), (3), Foot (4), McJunkin (6), Sabin (7), (8), Cunningham (9), (10), (11), Lewis and McCoy (12), Evans, Bowman and Winternitz (13), Gay and Morrison (14), and others. The fact that very few textbooks are now available which present the subject of the endothelial cell in a modern manner is an indication that there is no widespread recognition of the endothelial cell in pathological states. Furthermore, the complicated nomenclature at present applied to the endothelial cell is a source of confusion to readers of medical literature. It is to be hoped that the present interest in studies on the endothelial cell will result in making it as clearly understood and generally accepted as is the polymorphonuclear leucocyte. The recent work of Cunningham and Sabin (1924) on the monocytes opens a wide field for the study of this type of mononuclear cell in pathological states. Many inflammatory reactions are difficult of comprehension, and especially of explanation on a histological basis, without a proper understanding of the nature of the large mononuclear phagocytic cell of the exudate.

The researches of the last ten to fifteen years on problems of lung pathology, especially on the pneumonokonioses and on pulmonary tuberculosis as well as tuberculosis in general, have added much to our knowledge of the function of the endothelial cell. These pathological conditions lend themselves more readily to experimental investigation than do many other diseases in which the endothelial cell appears.

[1] From the Pathological Laboratories, University of Pittsburgh, Pittsburgh, Pennsylvania.

[2] Presented at a symposium on "The Endothelial Cell," arranged by the Medical Research Committee, before the Pathological Section of the twentieth annual meeting of the National Tuberculosis Association, Atlanta, Georgia, May 9, 1924.

In arranging the material which I wish to present, I have divided the discussion into three parts. As the basis for the first part I am using a resumé of my own studies (15), (16), (17), (18) on lung pathology, including studies of the "dust cells," of the mononuclear cells of the exudate in pneumococcic pneumonia and of the mononuclear cells in pleural exudates. For the second part, I am presenting certain outstanding features of the activities of the endothelial cell in pathological processes in general, based on personal observations in the study of human tissues. The third part is a review of some of the studies of Haythorn (2), (3), Foot (4) and others on the endothelial reactions in experimental tuberculosis, with reference to their bearing on the problems of human tuberculosis from a pathological viewpoint. It will, of course, be remembered that there are two great groups of endothelial cells to be considered, namely, the fixed endothelium of the blood and lymph vascular linings, and the wandering endothelial cells which are, according to current views, produced in great part by proliferation from the capillary blood-vessel linings. It is with the pathological importance of the second group that this discussion is chiefly concerned. The immunological aspects of the endothelial cell in connection with local or general tissue resistance will not be touched upon in this paper.

The studies of the "dust cell" referred to above were reported in 1920–1921. The problem of the identity of the phagocytic mononuclear cell of the lung alveolus is called to one's attention in studying lung tissues showing anthracosis. This work was really an elaboration of a study of anthracosis reported by Haythorn (2) in 1913, in which he expressed the view that the "dust cell" is an endothelial cell, probably originating from the blood or lymph-vessel linings. He further pointed out that carbon-loaded cells are capable of becoming sessile, when they are indistinguishable from connective tissue cells; but that when oedema is induced they round up and reveal their true nature. My work was directly stimulated by a paper by Sewell (5) supporting the epithelial nature of the "dust cell" and insisting on its origin from alveolar epithelium.

Quite simple experiments were carried out on rabbits. They consisted essentially of a combination of vital staining by isamine or pyrrhol blue with intratracheal injection of saline suspensions of finely ground carmine powder. A series of animal experiments was made, so arranged that it was possible to study the reaction to the carmine in the alveoli at periods varying from one hour to five days. The attempt was made to have the

short-period animals fairly well vitally stained by the intravenous administration of the benzidine dyes before introducing the carmine suspension into the lung. Blue vital dyes were used to avoid confusion with the black carbon particles in the "dust cells" of the animals, all of which show a mild degree of anthracosis. The india-ink method could have been used for, as a matter of fact, the occurrence of carbon particles in the lungs of these animals need not interfere with the use of india-ink suspensions as vital dyes, since the ordinary reaction with the suspension gives a much heavier loading of the phagocytic cells than ever appears in anthracosis in animals.

Without going further into technical procedures already reported, the result of these studies may be summarized. The carmine was phagocyted fairly rapidly, being practically all intracellular in twenty-four hours. This was accomplished by large mononuclear cells, a certain proportion of which also contained granules of the blue vital stain. These had arisen by proliferation of the capillary endothelium, which showed enlargement and blue granules in a certain number of the cells still *in situ*. The vitally dyed cells could be traced from the capillary wall into the alveolar spaces. Vital staining was less frequently encountered in the fixed endothelium in the controls receiving only vital stain than it was in those receiving intratracheal carmine injections. This indicated an increase in the local proliferation of endothelial cells as a response to the stimulus of particulate matter in the alveoli. There were no mitoses encountered in the capillary endothelium, though these were carefully sought. This was perhaps because the rate of proliferation of endothelial cells, as stimulated by the carmine in the alveoli, was not sufficiently active. In a later study of experimental pneumonia, in which india ink was used as a vital stain, mitoses were occasionally seen in the endothelial cells lining capillaries in the lung.

The subsequent wanderings of the carmine-loaded phagocytes, identified by vital staining as endothelial cells, are also of interest. They appeared to remain, for the duration of these experiments, in considerable numbers in the alveoli where they were seen as much enlarged, heavily loaded cells. A certain number, however, soon began to remigrate into the tissues with their loads of carmine, and gained the terminal lymphatics near the alveolar ductules. From here they migrated slowly toward the lymph nodes at the hilum, where they were first found 24 hours after the intratracheal injection.

It was felt that the process of anthracosis was paralleled in these experi-

ments; that the endothelial nature of the dust cell was demonstrated; and that the intracellular carriage of particulate substances into the lymphatic structures of the lung was conclusively shown. We believe that the disposal of tubercle bacilli from the alveoli may occur in an identical manner. This, if true, indicates intracellular transportation as a very important mode of actual introduction of the microörganisms into the body tissues. Also, by analogy, the probable mode of development of isolated tuberculous lesions in the peribronchial lymph nodes is indicated by these experiments.

In the study of experimental pneumococcus pneumonia (Permar, 1923) it was found, by the use of india ink as a vital stain, that the mononuclear phagocytes of the exudate were derived from the vascular endothelium. Desquamation or proliferation of the alveolar epithelium played no rôle in the production of mononuclears in the exudate. Moreover, these endothelial cells migrated into the tissues and along the lymphatics to the lymph nodes at the hilum, just as in the case of the carmine-bearing cells in the earlier work.

At present an experimental study is in progress in which the attempt is being made to determine the origin of the large mononuclear phagocytes appearing in the pleura in response to various mild irritants. The india-ink method of marking proliferating endothelial cells is being used in this work. The results up to this time indicate that, as Cunningham has already shown for the peritoneum, the serosal cells of the pleura are not proliferated save to restore the mesothelial lining. The phagocytic mononuclear cell called out in response to mildly irritating foreign substances introduced into the pleura, such as carmine or carbon suspensions, lanolin stained with sudan III, or lycopodium spores, is functionally and morphologically typical of the endothelial cell. Also a variable number of these cells in the local reaction is found to contain carbon granules. Trypan blue used as vital dye, with a carbon suspension in the pleura, shows cells of endothelial type bearing blue granules and phagocyting the black particles of carbon. The serosal cells, in all the experiments so far completed, have not shown phagocytic activity toward the materials present in the pleura; nor have they ever contained carbon granules, when that substance was used intravenously as a vital dye. Trypan-blue granules appear in the serosal cells, but they are few and are collected about the nucleus and not present as fairly large granules throughout the cytoplasm. These distinctions have already been described by Cunningham (10) and by Gay (14). Therefore, the evidence in this

work at its present stage points to the capillary endothelium as the source of the phagocytes dealing with particulate and other mildly irritating substances in the pleura. This finding is not in agreement with that of Karsner and Swanbeck (20), who believed that the serosal cells produced the phagocytes. In view of the most recent work of Sabin and Cunningham (8), (11), this, like many current views regarding the endothelial cell, may require modification.

According to our present views, we include under the term endothelial cell or endothelial leucocyte those cells variously described in the literature as the *large mononuclear cells, macrophage, clasmatocyte, histiocyte, resting wandering cell, wandering connective-tissue cell, adventitial cell, pyrrhol cell, cellule rhagiocrine,* and so forth. Foot (4) pointed out, in his first paper on endothelial reactions (1919), the difficulties encountered by a teacher of pathology when confronted with the problem of explaining the identity and origin of these cells. This agrees with our experience. Our next step is to summarize the important pathological states in which the endothelial cell is more or less prominent and in which still other special names have been applied.

A simple example is seen in the reaction of the endothelial cell to particulate foreign substances, to lipoid materials and to a wide range of foreign bodies in the tissues. Its reaction to particulate substances is illustrated in the phagocytosis by the endothelial cell of carbon particles and of blood pigment. These processes in the lung alveoli have given rise to two additional terms, the *dust cell* and the *heart-failure cell.* By the phagocytosis of liberated lipoid materials in the vicinity of disintegrating tissues or exudates, the cell becomes much enlarged and vacuolated, giving still other terms, the *compound granule cell* and the *foam cell.* In foreign-body granulomata, such as occur about relatively insoluble and inert substances in the tissues, the endothelial cell is active in the tissue response. Its most characteristic reaction is the development of the familiar foreign-body giant cell, which will be discussed further in connection with the tuberculous process.

In aseptic inflammatory reactions the endothelial cell appears quite early and has a definite importance, due to its phagocytic activity toward the debris of cells and fibrin in the injured area. In infected injuries the early exudate contains some endothelial cells, but the polymorphonuclear leucocytes soon predominate. It is only when the acute reaction is subsiding that the endothelial cell again appears. In the later stages of the reaction it is quite prominent as its phagocytic activities are essential to the progress of healing.

In chronic inflammatory reactions in certain special locations the endothelial cell is often present in definite collections in the tissues about the focus of reaction. Chronic salpingitis is a striking example. Here it is a common thing to find, upon gross examination, small opaque yellow masses among the adhesions about the tube and lying within the thickened glassy wall. Microscopic study shows these foci to be collections of large endothelial cells having a finely vacuolated cytoplasm (compound granule cells) due to the presence of innumerable globules of lipoid material derived from the disintegration of the exudate within the tube. The same finding is associated with chronic cholecystitis and, more rarely, with chronic appendicitis. Here the term *foam cell* has been used. The endothelial cell also appears in connection with bone repair and with chronic inflammation in body tissue, where it has long been known under the name of the *osteoclast.*

In certain inflammations due to specific microörganisms the endothelial cell forms the most important element in the reaction. Indeed, in these it is difficult to offer an adequate explanation of the reaction without an understanding of the part played by these cells and by the vascular endothelium in producing them.

First to be mentioned is typhoid fever. Here the endothelial nature of the essential cell of the exudate is now pretty generally recognized, perhaps because more than twenty-five years have passed since the first report by Mallory (19) of the histological reactions in this disease. It is sufficient to recall the enormous proliferation of large endothelial cells, showing marked phagocytic properties toward degenerated lymphocytes and other cells. These cells are actively produced by the vascular endothelium wherever stimulated by the toxin of the *B. typhosus.* They accumulate in the lymphoid structures of the intestine in such quantities as to seriously interfere with the local blood supply. This, combined with the tendency to narrowing or even occlusion of the small vessels by the proliferation of their lining endothelium, leads to the breaking down of the involved lymphoid structure, thus producing the typhoid ulcer of the intestine.

In syphilis the endothelial cell is present in certain numbers in the lesions in all stages, but in none is it so important as in the typical gumma. Here again it is necessary to recall that the mode of production of the endothelial cell is responsible for occlusion of a certain number of blood vessels. This fact explains the recurrent, irregular and relatively extensive necrosis occurring in gummata, which is, at least in great part, due to the peculiarities of the endothelial reaction.

The tissue reactions to the tubercle bacillus will form the subject of the remainder of the discussion. The human lesions are very well known. Their avascularity is perhaps their outstanding characteristic. The nature of the cells in the familiar zone of closely packed mononuclear cells, known as *epithelioid* cells, has been the point of greatest discussion. These have now been established as endothelial in nature and origin. Occlusion of vessels is much less marked in tuberculous reactions than in the others just described. The dense, closely packed endothelial cells of the typical tubercle undergo the necrosis characteristic of this lesion.

Foot (4), using a colloidal suspension of carbon as a vital stain, was able to show that the epithelioid cell is of endothelial origin. He believed that the greater number of these was developed locally by proliferation of the capillary endothelium, but at the same time he felt that the addition of a certain number of endothelial leucocytes from the circulating blood could not be ruled out. This applies to tuberculosis in any location. In a special study of experimental pulmonary tuberculosis Foot (4) also studied the importance of the respiratory epithelium, which, in agreement with other observers, he excluded as a factor in tubercle production. Carrying his studies further, Foot (4) investigated miliary tuberculosis, as well as tuberculosis of the central nervous system. He found that in lung, liver, spleen, kidney, lymph nodes, omentum, brain and meninges, the tubercles produced were composed chiefly of cells originating in the local capillary vascular endothelium. In the instance of the lesions of the central nervous system the evidence indicated that a definite proportion of cells going to make up tubercles was to be traced to the endothelial leucocytes of the blood stream. The endothelium of the liver, bone marrow and lung was most active in producing these phagocytes.

Having thus briefly outlined the present-day opinion of the nature of the essential cell of the tubercle, the nature and origin of the characteristic giant cell may be considered especially in relation to experimental studies. This cell is a type of foreign-body giant cell, the so called Langhans cell. There are two opinions held in regard to the mode of development of these multinucleated masses, one being that repeated mitosis without separation of the cytoplasm produces the syncytium; the other, that it is the result of a coalescence of numerous isolated cells. Foot (4) believes that mitoses may be found in foreign-body giant cells. He even states that multiple mitoses such as occur in neoplasms may be encountered. These were found by him in a study of acute aseptic

inflammation in the omentum. In connection with tuberculous inflammation, however, Foot (4) states that giant cells are formed by fusion of the endothelial cells. Haythorn (1913) (2) reported some pioneer experiments with the use of india ink as a mode of marking the endothelial cells, and has recently (1922) (3) reported a series of studies on experimental tuberculosis using similar methods. He injected tubercle bacilli and india ink into the outer margins of rabbit's ears. When the injected site showed definite thickening one ear was immersed in water at 65°C. for a few minutes to induce oedema; the other was used as a control. Twenty-four hours later the outer half of each ear was removed under ether and histological preparations were made. This detail is given in order that the findings regarding giant cells may be clearly understood. The tuberculous process was at a stage in which numerous giant cells had developed. Under the influence of oedema these structures were much enlarged and certain interesting details were revealed. The outer walls of the syncytial masses were sharply demarcated but the individual outlines of the various cells had disappeared. The amount of pigment present was variable but in many instances pigment granules were found arranged in characteristic fashion about the respective nuclei. Mitotic figures were not seen. This all pointed to the formation of multinucleated cells by fusion.

The foregoing summarizes the present-day conception of the activities of the endothelial cell in tubercle formation.

There remain for discussion some points bearing on (1) the primary entrance of the microörganism into the tissues; (2) the earliest reaction to its presence (or the early stage in the histogenesis of the tubercle); and (3) the subsequent spread of the infection from a primary focus to form both local and distant secondary foci.

Regarding the first of these points the lung offers a better site for an experimental study than does the gastrointestinal tract. At the same time it is difficult to reproduce the exact conditions found in spontaneous human tuberculous infection. Foot (4) employed extremely small doses of bacilli but produced fairly massive lesions. As he described them, they were evidently primarily destructive in nature, at the same time showing large numbers of endothelial cells. As vital staining by the india-ink method was used, these cells were identified by carbon granules. Their proliferation began as early as five hours after the intratracheal injection of tubercle bacilli. By the fourth day typical tubercles were found in the interstitial tissue, chiefly within small collections of lymphoid

cells. These tubercles were composed of endothelial cells, some of which contained carbon granules. The experiments of longer duration in this series need not be described, as they showed a gradual progressive development of more and more massive pulmonary tuberculosis.

The point to be brought out here is that the tubercle bacillus has been carried into the tissues from the finer air passages and alveoli by endothelial cells, in the same way that these cells carry particulate substances. Whether intracellular transportation also accounts for primary invasion of the intestinal tract is not certain, though it offers an explanation for the invasion of an intact mucosa. However, the structure of the intestinal mucosa admits of the localization of tubercle bacilli within crypts where a destructive process may precede the actual invasion of the tissue. We feel that in the lung the active phacogytic action of the endothelial leucocytes constantly present in the alveoli may result in the inclusion within these cells of the few microörganisms which are able to reach the alveoli in ordinary air-borne infection. Therefore, the endothelial cell is responsible for the actual introduction of the bacilli into the tissue in these cases, granted that the death of the cell is not brought about before remigration into the tissue has occurred.

After its entrance into the tissues, the primary reaction to the tubercle bacillus consists of a local accumulation of endothelial leucocytes, and soon a small giant cell appears. The tubercle bacilli may be demonstrated still in intracellular positions. In the giant cell they lie chiefly in that part of the cytoplasm farthest removed from the nuclei. The earliest development of necrosis is in the body of the giant cell. Lymphocytes are gradually attracted and fibroblasts stimulated to a variable degree. The fibroblasts, however, do not permeate the closely packed endothelial (or *epithelioid*) zone and new capillary formation does not occur. Hence, as stated at the beginning of the discussion of the tubercle, the focus is an avascular one and necrosis proceeds at its centre.

It is characteristic of this granuloma that, following an initial focus, secondary foci arise in the immediate vicinity which go through the same sequence of events and come to coalesce with the primary lesion; thus the area of destructive inflammation gradually enlarges. Not only are independent foci formed in the immediate vicinity but also at some distance from the initial lesion. The more distant ones follow the course of lymphatics and are usually found in the nearest lymph nodes. There is, of course, a third type of lesion following the primary focus, namely, that due to dissemination by the blood-stream.

Some experimental studies by Haythorn (3) have brought out very interesting and definite points regarding the rôle of the endothelial cell in giving rise to both local and more distant extensions from a primary tuberculous focus. His experimental evidence was in favor of the intracellular transportation by wandering endothelial phagocytic cells which migrated out from the original focus. He was able to show that these cells carry tubercle bacilli to neighboring tissues and also through the lymphatic channels to the lymph nodes, where they may give rise to new lesions. Less commonly they may gain entrance to the general circulation and give rise to distant foci n this way. Although tuberculous foci are sharply localized, it is possible that tubercle bacilli may become free in tissue spaces or lymphatics where they may be washed along in the fluids. It is certain that extensive dissemination of free bacilli occurs when they are so liberated into the blood-stream and into the serous cavities; but there is little experimental evidence to indicate that a microorganism, even though liberated as we have suggested, would long remain free, since not only wandering but also fixed endothelium is phagocytic for the tubercle bacillus.

Haythorn (3) injected a series of animals in the groin with a mixture of tubercle bacilli and india ink. These were killed at intervals varying from eight days to eighteen months. He found that the retrosternal lymph nodes were consistently tuberculous. In one instance, using a bovine strain, cells bearing pigment and tubercle bacilli were found in the sternal nodes on the eighth day. In another (human strain), a similar reaction was found thirteen days after inoculation. Typical early tubercles were commonly observed in these nodes after seventeen days. In those animals of seventeen days or longer duration tuberculosis also occurred in other organs but the only pigmented tubercles were those in the sternal nodes, which in the guinea pig are important in the drainage of superficial tissues of the groin. This clearly shows that not only had tubercle bacilli been carried from the original focus through the lymphatics to the sternal nodes, but that the great bulk of cells going to make up the tubercles in the sternal nodes had also migrated from the original focus, where black pigment was abundant. Hence, it is apparent that a strictly local origin for the majority of the endothelial cells going to form a tubercle is not found in every instance, but that they may be developed from capillary lining endothelium elsewhere and migrate for some distance to take part in tubercle formation.

CONCLUSIONS

From the above cited experimental work and discussion, the conclusion is reached that the function of the endothelial cell in various pathological states is that of phagocytosis of a wide variety of particulate materials and lipoid substances, including the debris of dead and disintegrating tissue cells and of the products of inflammation. Further, it is the prime element in the reaction to foreign bodies in the tissues, producing, by fusion of individual cells, the typical giant cell of foreign body granulomas.

With special reference to the function of the endothelial cell in tuberculosis, it appears that the endothelial cell primarily has to do with reactions to milder types of irritants which are thereby localized, and that of these the tubercle bacillus is one of the most important.

A knowledge of the various phases of endothelial cell reactions is essential to a comprehension of the anatomic tubercle and of the conglomerate tubercle.

Finally, it is evident that the endothelial reaction leading to localization of the tubercle bacillus is complicated by the fact that the endothelial cell also wanders for considerable distances in the tissues. Thus, intracellular transfer offers an explanation not only for the primary invasion of the microörganism and the local spread to form the conglomerate tubercle, but also for the development of distant secondary foci such as those in regional lymph nodes.

From the evidence in hand, we feel certain that cells of blood capillary endothelial origin can and do perform the functions just described. The recent work of Cunningham and Sabin (8) (11) would indicate that there is another mononuclear phagocyte, which may necessitate a restudy of many pathological processes in order to determine the relative importance of these two cells.

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THE PULMONARY LYMPHOID TISSUE IN OLD AGE[1]

WILLIAM SNOW MILLER[2]

In my paper on *The Distribution of Lymphoid Tissue in the Lung*, published in 1911, the thesis was advanced that "the quantity of lymphoid tissue increases from childhood to old age and that this increase is largely due to the irritation arising from the constant inhalation of irritating substances."

In the interval between the above publication and the present time I have been constantly on the watch for normal lungs from individuals sixty years of age and older. Obtaining this material has been more difficult than anticipated because the autopsy material available was limited, and because there are many chronic affections of the lungs that occasion the rejection of the material due to an increased production of lymphocytes. For example; the lungs from an individual ninety years old appeared, grossly, to be an excellent specimen from extreme old age. Sections, however, showed that there was a chronic bronchitis present in both lungs associated, in one of them, with a chronic inflammation of the pleura.

No attempt has been made to discuss pneumonokoniosis in individuals who have worked in dust-laden atmospheres. Every lung studied has been carefully selected.

In the publication above cited Sukiennikow's description of the tracheobronchial and bronchopulmonary lymph nodes was accepted. Further study has shown that his description of their character and situation agrees, in general, with the results which I have obtained from the lungs of adults and of old age. However, in those lungs which showed the greatest amount of pigmentation, the lymph nodes at the hilum and the bronchopulmonary nodes were increased in size and were highly pigmented; while in those lungs which were comparatively free from pigment these nodes were not greatly increased in size and showed but slight pigmentation.

[1] From the Anatomical Laboratory of the University of Wisconsin, Madison, Wisconsin.

[2] Aided by a grant from the National Tuberculosis Association.

While Sukiennikow called attention to the greater number of lymph nodes associated with the right lung, he did not call attention to the fact that there is a greater number of lymph nodes associated with the eparterial bronchus than with the bronchus which supplies the middle lobe or with that which supplies the lower lobe of the right lung.[3]

In the lungs of individuals thirty years old or younger, who have died from diseases other than pulmonary, I have rarely found a true lymph node beyond the point where the second ventral branch is given off from the main-stem bronchus. Beyond this point I have occasionally found a single lymph follicle (germ centre) in the angle between the main-stem bronchus and the third ventral branch; but usually only lymphoid tissue in greater or less quantity is present. In lungs from individuals sixty or more years old, there is a small lymph node in the angle formed by the main-stem bronchus and the third ventral bronchus, and the lymphoid tissue associated with the finer divisions of the bronchial tree is always increased in quantity; in case there is much pigment (carbon) present it may be so abundant as to obscure the amount of lymphoid tissue.

That the bronchopulmonary lymph nodes were situated in the angle formed by the branching of the bronchi was fully established by Sukiennikow; his description did not extend to the finer divisions of the bronchial tree, and the study of lymphoid tissue referred to above included that portion of the bronchial tree which was situated beyond the point where his description ended.

There are five important landmarks which assist in locating the situations in which lymphoid tissue is found within the normal lung; namely,

(1) At the place where radicles of the pulmonary vein arise from the pleura.

(2) Where veins arising from the distal end of ductuli alveolares join venous trunks situated on the periphery of the primary lobule (anatomical unit).

(3) Where veins arising from the neighborhood of the place at which bronchi or bronchioli divide join larger venous trunks which may, or may not, be situated in connective tissue septa.

(4) At the distal end of the ductuli alveolares.

(5) At the place where bronchi or bronchioli divide.

The accompanying diagram (fig. 1) slightly modified from that in

[3] The eparterial bronchus is distributed to the upper lobe of the right lung and gives origin to the apical bronchi.

the April, 1919, issue of the AMERICAN REVIEW OF TUBERCULOSIS, will assist in their location.

An increase in lymphoid tissue along the finer divisions of the bronchial tree, in individuals over sixty years old, is especially marked at the point where bronchioli divide into *bronchioli respiratorii*, and at the distal end of the *ductuli alveolares*. In the latter situation lymphoid tissue

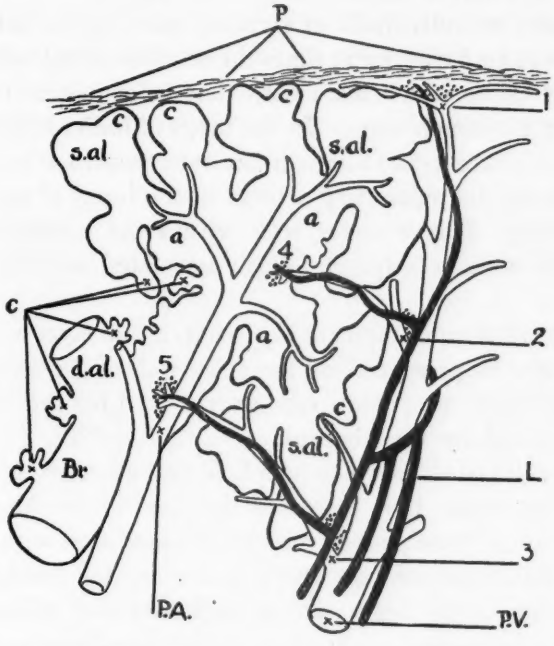

FIG. 1. SCHEMATIC LONGITUDINAL SECTION OF A PRIMARY LOBULE

Br., a bronchiolus respiratorius which divides into two ductuli alveolares; *d.al.*, only one of which is carried out in detail; *a.a.a.*, three atria; *s.al.*, sacculus alveolaris; *c.*, alveolus pulmonis; *P. A.*, pulmonary artery; *P. V.*, pulmonary vein; *L.*, lymph vessels. *1,2,3,4,5*, the five points mentioned in the text. The position of the lymphoid tissue is represented by the stippled areas. (After Miller, AMER. REV. TUBERC., Vol. iii).

is often recognized with difficulty in the lungs of individuals under thirty years of age; in old age, however, it is much more pronounced and the presence of pigment makes it still more distinct.

Besides these distinct masses of lymphoid tissue there is present, in old age, in the walls of the bronchi and the larger bronchioli, situated between the epithelium and the smooth muscle, a delicate layer of diffused lymphoid tissue.

It is often difficult to determine whether a given mass of lymphoid tissue belongs to the bronchus or to the accompanying pulmonary artery. Because of this difficulty, an arbitrary classification was made, in my previous paper, by which masses of lymphoid tissue lying between the artery and bronchus were considered as belonging to the bronchus, while those masses situated between the artery and the adjoining air spaces were considered as belonging to the artery.

In the lungs of individuals of sixty or more years, this distinction does not always hold true, for at times the artery is completely surrounded by lymphoid tissue which fuses with that belonging to the bronchus, thus forming a common mass. In the lungs of individuals under thirty years of age it is rare to find a sheath-like arrangement of lymphoid tissue extending along the pulmonary artery; in the lungs of old people it is not uncommon. I have never seen within the normal lung, at any age, a lymph node or a lymph follicle associated with the pulmonary artery.

In old age, when much pigment is present, a thin layer of diffused lymphoid cells may be present along the outer wall of the finer divisions of the pulmonary artery. Unless especially looked for the lymphoid cells may be obscured by the pigment.

In all those situations in which lymphoid tissue is found associated with the pulmonary veins, it is increased in quantity in old age. This is especially true of those masses which are associated with veins which arise from the bronchial tree and join the venous trunks situated in the connective tissue septa which mark out the secondary lobules (fig. 1, 3).

Besides these masses of lymphoid tissue which are directly associated with the veins small collections of lymphoid tissue are scattered throughout the septa which have no direct relationship to radicles of the pulmonary vein. These isolated masses are usually found where alveoli that are in the direct line of the air current abut against the septa.

In my previous paper on lymphoid tissue in the lung attention was called to the fact that for the first three weeks of life the pleura did not show any pigmentation, and that the amount of lymphoid tissue was small; but after that time the pleura showed an increased amount of pigment and, *per consequens*, an increase in the amount of lymphoid tissue.

In the pleura of individuals who have lived until old age in an atmosphere in which carbon or other particles of dust are suspended, the

lymphoid tissue of the pleura is much increased in those situations in which it is normally present.

In a preceding paragraph small masses of lymphoid tissue were described in the septa between the secondary lobules independent of any relationship to the pulmonary vein. Such masses are much more frequent in the pleura. Here they are often seen situated between a small pleural lymph vessel and the rounded tip of an alveolus located just beneath the pleura. These small masses of lymphoid tissue usually contain a considerable quantity of pigment (carbon). It is not uncommon to find phagocytes laden with particles of carbon, which they have picked up within the alveolus, lying close to, or just penetrating, the

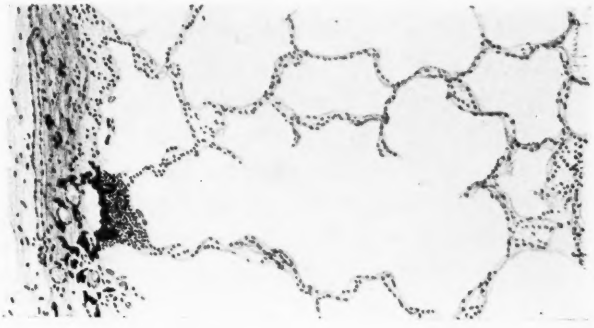

FIG. 2. A SMALL MASS OF LYMPHOID TISSUE WITHIN THE PLEURA AND SITUATED BETWEEN A PLEURAL LYMPH VESSEL AND AN AIR-SAC

Note the amount of pigmentation and the pigment-laden phagocytes just within the air sac. × 50.

wall of an alveolus, on their way to deposit their load in the lymphoid tissue (fig. 2).

In other instances these small masses of lymphoid tissue were associated with a radicle of a pulmonary vein which was situated on the periphery of a primary lobule and had its origin from the capillary network in the walls of the air-sacs just beneath the pleura.

It is interesting to note that in many points the results of this study of lymphoid tissue in the human lung, in old age, coincide with the results obtained by Gardner in his study of experimental pneumonokoniosis, and by Willis in his study of spontaneous pneumonokoniosis in guinea pigs.

In conclusion, it can be stated that there is, in old age, a definite increase in the lymphoid tissue within the lung independent of that which may be produced by inflammatory diseases, and that the amount of this increase is dependent on the amount of carbon, or other irritating particles inhaled.

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SPONTANEOUS TUBERCULOSIS IN GUINEA PIGS EXPOSED TO BREATH-POLLUTED AIR[1]

HENRY SEWALL AND MAX B. LURIE

The term "spontaneous" tuberculosis characterizes disease which is not intentionally induced. A more properly descriptive adjective would be "accidental" or "nonexperimental." For none can doubt that implantation and multiplication of tubercle bacilli in the body is the *sine qua non* of the tuberculous state. The disease does not arise *de novo*. It is worth while to repeat this platitude, for in the famous controversy which first established Pasteur as a biologist "spontaneous generation" was exact language; it meant the origin of life where there was no life before.

Perhaps most laboratory workers assume that guinea pigs, despite their phenomenal susceptibility to artificial inoculation with tubercle bacilli, so rarely, if ever, develop tuberculosis spontaneously that the accident may be left out of account in experimental statistics.

Susceptibility of guinea pigs to tuberculous infection: It is useful to define with exactness the grade of susceptibility of the guinea pig to inoculation with tubercle bacilli. Römer and Joseph (1) quote the estimate of Findel that a mass of one centigram of tubercle bacilli contains about 400,000,000 single bacilli; and they calculated that their own inoculations of guinea pigs, by the subcutaneous and intraperitoneal routes, were effective in dilutions which represented but four bacilli with each injection. They present reasons for believing that tuberculous disease in the guinea pig may be engendered by a single virulent bacillus, especially if of the bovine type. Fraenkel and Baumann (2) also suspect that with many cultures of tubercle bacilli the implantation of a single germ is capable of causing tuberculosis in the guinea pig. They subjected such animals to the inhalation of sprays containing tubercle bacilli in concentrations of 1 in 1000 millions to 1 in 100,000 millions, with positive results. The stronger suspensions caused the death of guinea pigs in

[1] From the Research Department of the National Jewish Hospital for Consumptives, Denver, Colorado.

six weeks. After the weaker doses the interval before death was prolonged and could reach seven to nine months. Bartel and Neumann (3) also produced inhalation tuberculosis in guinea pigs by exposing them for two to five minutes to sprays of dilute suspensions. They concluded that infection thus induced operated both through the respiratory and the digestive tracts; but they were convinced that the lungs and bronchial lymph nodes presented loci of least resistance for the development of tuberculosis. They quoted the inhalation experiments of Preyss (4) with tubercuous sputa, in which positive results were obtained with an estimated number of forty bacilli. Preyss made an important contribution respecting the conditions of inhalation-inoculation; he found that positive results were obtained most easily, if at all, when mechanical injury was done to the air passages, as by the inclusion of steel dust in the inhalations.

Corper (5) has published observations on the number of tubercle bacilli contained in a given weight of cultures of the micröorganism and his results differ widely from those previously obtained by Findel. He studied ten different cultures of tubercle bacilli, grinding a given weight of bacilli in a few drops of salt solution to form suspensions which were diluted to various degrees. The bacilli were very prone to clump in groups of six to ten individuals. The germs were counted in films against red blood corpuscles, after the method of Wright. Corper estimated that each milligram of culture contained from 5.01 to 7.56 *billions* of tubercle bacilli.

The present authors have been engaged in a study which bears upon this discussion. It was desired to trace the development of tuberculosis in guinea pigs after their inoculation with a minimal infecting dose of a virulent culture. Dr. Corper kindly prepared for us suspensions in which it was estimated that each cubic centimetre of normal salt solution contained one billionth of a milligram of bacilli. He injected subcutaneously in the abdominal wall 1 cc. of the suspension into each of 100 young male guinea pigs.

With the exception of one guinea pig, which died five days after its inoculation, every animal developed tuberculosis as proved by autopsy. In the only case that might have been regarded as doubtful, an animal dying 26 days after inoculation, tubercle bacilli were demonstrated in smears from a lymph node.

There can be no doubt that the positive results of our inoculations uphold the bacillary-weight estimate of Corper as opposed to that of

Findel. According to the former, each of our doses contained an average of about 6 bacilli, while each dose according to Findel could only have contained an average of one twenty-fifth of one bacillus. It is worth noting that our guinea pigs were injected in two lots of 50 animals each, at an interval of 67 days.

It was noted that one of these lots presented clinical evidences of having received a less virulent dosage than the other. It was then found that, though each lot had been inoculated from the same strain of bacilli, in the one case the culture was only about four weeks old while in the other it was about eight weeks old when used. The older culture apparently produced, on the whole, a milder disease.

Frequency of spontaneous tuberculosis in guinea pigs and conditions inducing it: We may touch upon the frequency of so called spontaneous tuberculosis in guinea pigs as portrayed by a few observers. Bartel and Spieler (6) could report, after a long experience, only three cases of spontaneous tuberculosis in guinea pigs and these all in old animals with anthracotic, and therefore probably injured, lungs.

Bartel (7) quotes Cornet as having inoculated with tubercle bacilli 96 gravid guinea pigs whose offspring, observed for five weeks after birth, showed no symptoms of disease. But Bartel himself inoculated a female guinea pig two days after giving birth to a litter of three. These offspring, having been suckled by their mother, were killed 31 to 41 days after birth and tubercle bacilli were found to be present in the lymphatic organs of all.

Cobbett (8), in his excellent treatise says, "It is the rarest thing to find a tuberculous guinea pig among those bought for research;" while Calmette (9) remarks that "the guinea pig never, or hardly ever, acquires tuberculosis spontaneously."

Remlinger (10), at the suggestion of Calmette, has recently submitted to experimental investigation the conditions under which guinea pigs "spontaneously" contract tuberculosis. He confined for several months healthy guinea pigs in the same cage with others having tuberculous ulcers. Five of the normal animals contracted the disease while thirty escaped it. Normal guinea pigs were confined with tuberculous ones not affected with skin ulcers until these died; three of the former contracted tuberculosis while at least forty escaped. Except in a single instance, however, he never saw the contagion transmitted from sick to well guinea pigs unless they were closely associated in the same cage.

Normal guinea pigs kept their health when placed in cages in which others had recently died from generalized tuberculosis. Fifty-two guinea pigs were fed for a year exclusively on barley soiled each day with fecal matter from tuberculous guinea pigs, but failed to develop disease.

Tuberculous guinea pigs with open ulcers are apt to infect normal guinea pigs in close association with them in about one out of five to six cases; when there is no ulceration of the skin the contagion is transmitted in only one out of twelve or fifteen cases.

But we must return to the master, Robert Koch, for a circumstantial account of the conditions on which spontaneous tuberculosis in guinea pigs depends (11). He states that out of many hundreds of rabbits and guinea pigs bought for experimental purposes and finally sectioned there had never been found a tuberculous animal. Plain symptoms of tuberculosis hardly ever developed in such animals until they had been confined in the close vicinity of tuberculous animals for at least three to four months. It was noteworthy that the number of cases of spontaneous tuberculosis that developed among his normal animals rose and fell with the number of animals in proximity with them having experimental tuberculosis. The postmortem findings in cases of spontaneous tuberculosis were characteristic. There were regularly, in such cases, one to several large tuberculous foci, more or less caseated, in the lungs and bronchial lymph nodes; sometimes the infection involved only the bronchial nodes. The tuberculous involvement of the other organs was only moderate and but slightly progressive. We note with surprise, however, Koch's statement that when tuberculosis is induced by the subcutaneous injection of tubercle bacilli in the abdominal wall the bronchial lymph nodes, if by these is meant the tracheobronchial nodes, remain hardly discoverable while the liver and spleen are in an advanced stage of tuberculosis. Perhaps our own very different findings depend upon the minuteness of our infective doses.

Among his animals which developed tuberculosis spontaneously Koch investigated 17 guinea pigs. The detailed account of the pathological changes in these animals forms an important contribution to the subject. Koch strongly emphasizes the necessity for the prophylaxis of spontaneous tuberculosis in the animal room. This involves the segregation of the tuberculous from other animals in different cages, with frequent cleansing of the latter. It is not advisable to confine normal rabbits and guinea pigs in the vicinity of tuberculous animals, for they can scarcely remain much longer than eight to ten months in infected quarters without

developing tuberculosis. In one of his experiments on immunity it was desired to maintain a number of animals alive as long as possible but, in spite of every care, only a few remained free from tuberculosis longer than a year and these succumbed to the disease some months later.

After these experiments, continues Koch, it is obvious that all the many experiments which take account of the presence of tuberculosis in animals after they have been maintained three months or more are little to be relied upon unless the development of spontaneous tuberculosis can be excluded.

PERSONAL OBSERVATIONS

The observations of Koch on the frequency and prophylaxis of spontaneous tuberculosis have been in print for more than forty years, but there is reason to believe that his warnings are not seldom neglected. Nevertheless, we probably would not have ventured to detail our experiences were it not that the very high incidence of spontaneous tuberculosis among our guinea pigs may possibly be accounted for by the fact that all our animals had been subjected to a definite experimental environment, one of an exceptionally breath-polluted air, the hygienic effects of which it was our purpose to investigate. Whether our cases of spontaneous tuberculosis were in fact superinduced by the conditions of our experiments on ventilation is a weighty problem which we hope in time to solve; in the meanwhile it seems proper to present these fortuitous occurrences in a preliminary communication.

The present article is based upon experiences which were wholly unexpected and involved a considerable number of normal young male guinea pigs which had been submitted to experimentation during the period included between December 1, 1921, and August 18, 1922. The investigation mentioned has already been described (12). Its purpose was to determine whether guinea pigs rebreathing air polluted by their own kind were thereby sensitized, so as to respond with anaphylactic symptoms when reëxposed to the same conditions after an appropriate interval.

The foulness of the rebreathed air was estimated by its content of carbon dioxide which was allowed to reach about 9 to 13 per cent in the experimental bell jars. Each experiment lasted between one and a half to two and a half hours and terminated after the production of intense dyspnea. Each animal was usually submitted to two or three exposures

within three to five days and again to a single exposure after three to five weeks. None suffered any apparent injury. During and after the conclusion of the research the guinea pigs were, for the most part, stored in small metal cages, about 18 x 13 x 10 inches in dimensions, and two in each cage. The bell jars in which the experiments were conducted were used in alternation with a different investigation involving guinea pigs infected with tuberculosis, some of which developed open ulcers at the site of inoculation in the left groin.

The jars and their floors were usually, but not always, well washed, not sterilized, after each experiment. The cages used for storing the animals had long been in use without sterilization. For several months during the early life of our animals the air of the overcrowded animal room, as judged by its odor, was highly tainted. Later, this condition was thoroughly corrected. None of the numerous guinea pigs belonging to other workers in the laboratory, and stored under similar conditions as ours, developed spontaneous tuberculosis.

Unfortunately, the individual identification of most of our experimental guinea pigs was lost after they had been put in storage, so that it was impossible to certify to their exact ages and experimental histories.

The writer was absent from the laboratory during six weeks in December, 1922, and January, 1923. On his return it was found that a considerable number of the guinea pigs from the experiments which have been detailed had died and had been submitted to autopsy. Of 37 guinea pigs dying up to January 17, 1923, nine were recorded as presenting definite macroscopic signs of tuberculosis and 9 others showed suspicious evidences of the same disease. By an unfortunate error a microscopic study of these decedents was neglected. It should be noted that these autopsies were made by a laboratory assistant who, though reliably experienced, was not familiar with the details of our research and took it for granted that our animals had been purposely infected with tuberculosis. These autopsy records were, therefore, only of value in stimulating a more exact conduct of further observations and it is on these that the present report is founded. Our animals which survived after January, 1923, eighteen in number, were apparently, with two exceptions, all from a group that had received their experimental exposure to rebreathed air in July and August, 1922. From March 5 to December 1, 1923, eight of our guinea pigs died and, on autopsy, 4 of them presented macroscopic signs of tuberculosis as recorded below, and acid-fast microör-

ganisms, wholly resembling tubercle bacilli, were demonstrated in smears or sections from their organs. This, of course, excludes the suspicion of "pseudotuberculosis." Two others were killed on November 8, and both were found to be tuberculous. Ten others belonging to our suspected group died or were killed within this period and were recorded as being free from tuberculosis. It should be said that in three of these the macroscopic evidences of tuberculosis were pronounced, but tubercle bacilli could not be demonstrated in their tissues which had been preserved in 10 per cent formalin.

The deaths of our guinea pigs occurred under such conditions and at such periods that no etiological study further than the microscopic demonstration of the bacillus was attempted. However, about December 1, the 5 remaining animals of our suspected group were killed by illuminating gas and autopsied after we had made definite arrangement to inoculate normal guinea pigs, as well as culture tubes, from suspected organs. It chanced that all five of these guinea pigs failed to show any macroscopic evidence of tuberculosis.

POSTMORTEM EXAMINATIONS OF GUINEA PIGS WITH SPONTANEOUS TUBERCULOSIS

1: Died March 5, 1923. Lungs thickly studded with tubercles 0.1 mm. in diameter. Spleen and liver much diseased. Tubercle bacilli numerous in sections of tissues.

2: Died October 30, 1923. This guinea pig, apparently normal when removed from cage and placed under observation jar, within five minutes gasped and died. *Autopsy:* Blood clot over liver, which is yellow and very large and apparently tuberculous. Spleen enormous, studded with gray-yellowish areas. Bloody effusion in each pleural cavity; suspicion of tubercles in lungs—not certain. Tracheobronchial nodes very greatly enlarged. Inguinal and retroperitoneal nodes normal. Smears from tracheobronchial nodes and spleen positive for tubercle bacilli.

3: Gassed November 8, 1923. Great pad of retroperitoneal fat, as usual. Spleen normal size but suspicious of tuberculosis; buried in fat and adherent to abdominal wall. Liver shrunken, dotted with whitish circles and adherent to diaphragm. Lungs and tracheobronchial nodes negative except old pleural adhesions of anterior left lung. An abdominal node at the pylorus has suppurated and another under right lobe of liver has formed an abscess nearly 2 inches in diameter. Smears of pus show many tubercle bacilli.

4: Gassed November 8, 1923. An enlarged node in left groin. Retroperitoneal nodes enlarged. Spleen enormous and thickly studded with

grayish areas. Liver large and spotted with yellowish areas; one edge necrosed. The anthracotic lungs contain small widely scattered tubercles. Tracheobronchial nodes enormous. Smears from several nodes show many tubercle bacilli.

5: Died November 17, 1923. Retroperitoneal nodes enlarged but inguinal and mesenteric nodes not palpable. Spleen enlarged, spotted with caseous areas. Liver large, pale, spotted with green-yellow areas. Lungs show pneumonic areas; a few small tubercles and a caseous margin. Tracheobronchial nodes enormous. Smears from caseated lung show many tubercle bacilli.

6: Died November 25, 1923. No enlargement of inguinal or abdominal lymph nodes. Spleen very large, with small tubercle-like spots. Liver large and fatty. Tracheobronchial nodes enormous and hard, and cut surface exudes pus. Substernal nodes enlarged and with caseous pus. Lungs packed with single and confluent tubercles. Smears from lungs, tracheobronchial and substernal nodes show many tubercle bacilli.

With one exception, no. 4, none of the above animals showed enlargement of the inguinal nodes, thus excluding the possibility of artificial inoculation. Their confinement without exercise in small cages may partly account for the excessive development of subcutaneous and subperitoneal fat which was a common character.

Their confinement was probably also the basis of the remarkable physiological asthenia which apparently led to death of guinea pig 2. Another animal, in which tuberculosis could not be demonstrated, also suddenly died while being weighed.

DISCUSSION AND SUMMARY

It is highly probably that the considerable number of guinea pigs which died during the writer's absence from the laboratory, and which were recorded as showing macroscopic evidences of tuberculosis, were in fact victims of this disease.

It is certainly noteworthy that in one-third of the remaining 18 animals tubercle bacilli were demonstrated in abundance.

At the time of death all the guinea pigs (55 in number) which had been preserved after being employed in the experiment on rebreathed air had been in close confinement for about 7 to 18 months. It is possible that the development of spontaneous tuberculosis among them was simply due to an environment the dangers of which Koch had so trenchantly pointed out. On the other hand the suspicion is obvious that the

drastic, though apparently harmless, subjection of the creatures to highly polluted rebreathed air, inducing intense dyspnea, was a predisposing factor in their disease. If so, it could have operated in at least two ways. First, the respiratory apparatus may have suffered traumatism as result of our experiments. Many autopsies have shown us that such experiments can induce the formation of petechiae in the lungs or even more or less extensive hemorrhagic extravasations. Again, a more or less intense grade of anthracosis is manifested by all long-stored pigs and, as pointed out by Bartel, this may signify lung injury inviting the development of tuberculosis. Second, the implantation of the tubercle bacillus may be determined not by traumatic injury to the air passages but by a vital degradation of that usually effective barrier in the guinea pig against infection, the "first line of defense" offered by the respiratory epithelium. This immunological reaction is one we dare not assume without definite foundation,—nor can it be dismissed on *a priori* grounds. Experiments designed to elucidate this problem, initiated some months ago, are still in progress.

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GAS REQUIREMENTS OF THE TUBERCLE BACILLUS[1]

GERALD B. WEBB, CHARLES H. BOISSEVAIN AND CHARLES T. RYDER

That the tubercle bacillus is an obligatory aerobe is well known. Of late some attention has been given to its other gas requirements and its behavior when deprived of oxygen.

The loss of virulence of bacilli which occurs when tuberculous animal tissues, especially lymph nodes, are incubated in normal salt solution at about body temperature, has been reported from our laboratory (1) (2) (3) (4) (5). In a fresh state such tissues generally produce the usual acute tuberculosis when planted under the skin of healthy guinea pigs. After a few days' incubation they produce a chronic tuberculosis which may last more than two years. After being incubated for a week or two they produce no disease at all, and the bacilli appear to be dead. At icebox temperature the phenomenon occurs very slowly if at all.

Similar facts observed several years ago by Bartel and his associates (6) (7) (8), in the case of tubercle bacilli introduced into normal lymph nodes and then incubated, were attributed by him to some specific bactericidal virtue of lymphoid tissue. However, we obtain the same results with pieces of tuberculous liver, and we have always thought it probable that they are due to deprivation of oxygen analogous to that which occurs at the bottom of culture tubes of broth to which bits of tissue have been added.

Recently we have made parallel experiments with emulsions of tubercle bacilli from cultures. The tubes containing the salt-solution emulsions are placed in pyrogallic sodium-hydroxide jars and incubated, and the attenuation occurs at about the same rate as in incubated tissues, while emulsions kept in similar anaerobic jars in the icebox are still fully virulent after three weeks. Control emulsions kept in the incubator but not deprived of oxygen remain virulent, though their virulence after three weeks' incubation appears to be somewhat less than that of the emulsions kept anaerobically in the icebox.

[1] From the laboratories of the Colorado Foundation for Research in Tuberculosis, Colorado Springs, Colorado.

It is possible that the phenomenon is more complex than it appears. Corper, Lurie and Kretschmer (9) have found the juices of incubated tissues bactericidal for tubercle bacilli under experimental conditions which make it improbable that the effect is a simple reduction. The exhaustion of oxygen by the pyrogallic method is of course not absolute. In the experiments with emulsions the bacilli may produce substances toxic to themselves, including, as Corper suggests, carbon dioxide.

Corper, Gauss and Rensch (10), following up some observations of Wherry and Ervin (11), find that tubercle bacilli are preventedf rom growing by a carbon-dioxide concentration equivalent to that which prevails in human tissues (5 to 6 per cent gas volume), and are killed by a few weeks' exposure to an atmosphere containing 12 to 15 per cent of carbon dioxide. They also report that the bacillus will not grow in the complete absence of carbon dioxide.

In studying this point we find that cultures on glycerine-agar, incubated in sealed jars containing some 40 per cent potassium-hydroxide solution, are inhibited; however, if glycerine-broth cultures are placed in the same conditions they grow vigorously. The failure to grow in the first instance is quite clearly due to the drying which accompanies the absorption of carbon dioxide by this means.

Oxygen, in fact, appears to be the only gas which is essential to the normal life and growth of the tubercle bacillus, if we except moisture. Cultured in glycerine broth in an atmosphere of pure oxygen, the bacillus grows well but the growth, instead of remaining on the surface, as it does in air, tends to sink to the bottom of the flask. This presents a suggestive analogy to some of Rosenow's observations on streptococci (12). He finds that in tall tubes of broth, with a piece of tissue at the bottom, these microörganisms grow at the level of optimum oxygen tension, which varies for different strains. In mixtures of air and nitrogen we find that the growth of the tubercle bacillus in glycerine broth varies directly with the percentage of air, and apparently ceases when this is reduced to about 20 per cent.

If anything is to be hoped for in the prevention and treatment of tuberculosis by vaccination in the traditional sense, asphyxiation may possibly be a favorable method for preparing killed or attenuated suspensions. Bartel from his early experiments was led to believe that animals which received tubercle bacilli from incubated tissue showed changes in their subsequent resistance to virulent infection, and we have some observations which seem to support this opinion. A

group of six guinea pigs which had received tuberculous tissues, incubated eight and ten days with apparently complete loss of virulence, were inoculated several months later with virulent bacilli; they lived on an average four months, which is a month longer than the usual life of our guinea pigs after virulent inoculation and nearly two months longer than two controls inoculated at the same time. Two of them showed healing of their ulcers of virulent inoculation, which we have never seen occur after first inoculation with virulent bacilli in normally susceptible guinea pigs. However, the effectiveness of the immunity

TABLE 1

Growth of human tubercle bacilli in various gases

CULTURE	ATMOSPHERE	RESULT
Human tubercle bacilli in 2 per cent glycerine broth	Air minus carbon dioxide (40 per cent potassium hydroxide)	Fair to vigorous growth
Human tubercle bacilli on 6 per cent glycerine agar	Air minus carbon dioxide (40 per cent potassium hydroxide)	No growth, dried out
Human tubercle bacilli in 2 per cent glycerine broth	Pure oxygen	Good growth, sinks to bottom of flask
Human tubercle bacilli in 2 per cent glycerine broth	20 per cent air, 80 per cent nitrogen	No growth
Human tubercle bacilli in 2 per cent glycerine broth	40 per cent air, 60 per cent nitrogen	Doubtful
Human tubercle bacilli in 2 per cent glycerine broth	60 per cent air, 40 per cent nitrogen	Some growth
Human tubercle bacilli in 2 per cent glycerine broth	80 per cent air, 20 per cent nitrogen	Fair growth

changes which result, even from actually healed or well-resisted first infection with tuberculosis in human subjects, is so dubious, and the risk involved in vaccination with living microörganisms, however attenuated they appear to be, is so great, that we probably should not expect too much from such procedures.

CONCLUSIONS

1. Human tubercle bacilli require an atmosphere containing a fairly high percentage of oxygen in order to grow.

2. Oxygen is the only gas required in appreciable amounts.

3. When tubercle bacilli are incubated in salt solution in the virtual absence of oxygen they lose virulence in a week or two, just as they do

when incubated in tissues. This phenomenon does not occur at icebox temperature.

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A TRIAL OF TWORT'S GLYCEROL METHOD FOR THE ISOLATION OF TUBERCLE BACILLI[1]

MAX B. LURIE AND JACK KIRSCHSTEIN

The cultivation of tubercle bacilli from tissues and contaminated materials has undergone numerous technical changes since the discovery and isolation of the bacillus by Robert Koch. His successful isolation was primarily due to the utilization of a solid medium, inspissated serum, which served admirably when contaminators were either absent or were first removed by passing the material through the guinea pig. This method required a wait of a month or more before attempting cultural isolation. Glycerol-agar was soon found to be a suitable medium for making subcultures and, finally, in 1902 Dorset (1) introduced the inspissated egg medium which proved satisfactory for primary cultivation. Innumerable attempts were then made to do away with the time-consuming guinea-pig inoculation to remove contaminators by utilizing chemicals for this purpose. Among the earlier and more noteworthy of these were the formalin (Spengler) and antiformin (Griffith) methods. The formalin method never achieved a widespread use, but Griffith's antiformin method (2) proved fairly successful in the hands of many students of tuberculosis and was the method of choice until in 1915 Petroff (3) devised his sodium-hydroxide method.

This method has been accorded almost universal acceptance and, although modified slightly by individual students to meet their own requirements, is still used in its original form. It consists essentially in exposing the material to be cultured for tubercle bacilli to an equal volume of 3 per cent sodium hydroxide for 20 minutes with frequent shaking at incubator temperature. The subsequent centrifugate is then either washed, to free it from alkali, or it is neutralized with hydrochloric acid before seeding the bacilli on a gentian violet-egg medium. The purpose of the gentian violet is to inhibit the development of such contaminating microörganisms which may not have been destroyed by the sodium-hydroxide treatment. The necessity for centrifugation

[1] From the Research Department, National Jewish Hospital for Consumptives, Denver, Colorado.

involves a certain waste of time, and it was probably this factor which led Griffith to do away with centrifugation in his method and seed the entire antiformin-sputum mixture on the medium directly. One of us found that this method did not prove, however, equal to Petroff's. Obviating of the centrifugation was, at any rate, a factor which seemed worthy of study. If a substance could be found which, though destructive to contaminators, would be innocuous for tubercle bacilli this might easily be achieved.

Glycerol has been variously used as a preservative and would appear, *a priori*, to possess possibilities along this line. In 1922 Twort (5) reported, briefly, experiments which indicated that glycerol possessed exactly the desired properties necessary for direct seeding. He states

> as a means of isolating acid-fast bacilli from contaminated material glycerine is extremely useful. Its ease of manipulation and its efficacy appear to be infinitely superior to the chemicals which have previously been utilized for this purpose. Tubercle bacilli in tissues, such as lymphatic glands, liver, spleen, lungs, preserved in pure glycerine, in cold storage, remain alive for months, and possibly for years. Preserved in 50 per cent glycerine in saline, the survival is often not longer than two to four months. Again, at room temperature death of the bacilli seems much quicker, and although the effect of incubator temperature on such tissues has not been tried, one assumes that it would aid considerably in the destruction of the bacilli. Pure cultures of acid-fast bacilli do not resist the action of the glycerine so well as when the bacilli are present in tissues. Ordinary bacteria will also tolerate glycerine to a certain extent, especially in the cold, and thus it has been found that for isolating tubercle bacilli from sputum, etc., room temperature is more suitable. It is probable that incubator temperature will be found to be better still, and I have already isolated tubercle bacilli from sputum which has been inoculated with glycerine and kept at 20°C.

The method as outlined briefly by Twort is

> A large platinum loopful of sputum or other material, from which acid-fast bacilli are to be isolated, is inoculated into tubes containing 1 cc. of pure glycerine, 75 per cent, 50 per cent, and 25 per cent glycerine in normal saline. After remaining for 24 hours at room temperature, cultures are made onto Dorset's 4 per cent glycerine-egg or Petroff's medium. If contaminations are numerous on all the tubes, further cultures are made on the third day, but this is, of course, not necessary when only one or two contaminations are present on the tubes. Sometimes all contaminating bacteria are destroyed after 24 hours in glycerine, but more frequently they are not all destroyed,

and the tubes may be very heavily contaminated. It may be necessary to revert to a third culture after a week; but the tubercle bacilli themselves do not appear to survive for longer than three or four weeks. A sufficient number of isolations have not yet been carried out to allow one to satisfy oneself as to the most suitable dilution of glycerine, and the most suitable temperature to use. It is probable that a fairly concentrated solution will be found to be most efficacious, with a temperature somewhere in the neighborhood of 20°–30°C. Latterly, in order to simplify the process, a quantity of pure glycerine equal to that of the sputum contained in the bottle is added, and after thorough mixing the bottle and contents are placed at 20°C. and cultures subsequently made.

Twort claims that "So far, by the use of glycerine, I have not once failed to isolate, with extreme ease, the tubercle bacillus from any specimens in which the bacillus has been demonstrated microscopically."

This report by Twort left much to be desired in the way of detailed information, yet his enthusiasm and encouragement indicated that glycerol possessed the properties required for destroying contaminators while at the same time it was an essential requirement, in small amounts in the medium, for the growth of the tubercle bacilli, especially of the human type, it being customary to add glycerol to 5 per cent concentration for this purpose. The method also eliminated the time-consuming neutralization and centrifugation of the previously described successful techniques. In Twort's method as described, however, any gain in eliminating centrifugation, and washing or neutralization, was counterbalanced by the necessity for making numerous cultures and from numerous glycerol dilutions. If the method was to possess any advantages over Petroff's method there should be a range of glycerol and a time interval under set conditions of room or incubator temperature, in which the contaminators would be destroyed and the tubercle bacilli remain alive. It therefore seemed advisable first, to test the effect of different concentrations of glycerol for different time intervals, and under different temperature conditions of room and incubator, upon suspensions of pure cultures of tubercle bacilli. For this purpose suspensions of four different strains (*Human*, an avirulent human tubercle bacillus, *Gluckson*, a virulent human tubercle bacillus, *Bov. D.*, an avirulent bovine bacillus and *Bov. Vir.*, a virulent bovine bacillus) of tubercle bacilli were made so that each cubic centimetre of suspension contained 5 mgm. of bacilli in sterile 0.9 per cent sodium-chloride solution. These suspensions were then mixed with three, one, and one-fourth volumes

TABLE 1

The growth of tubercle bacilli following exposure at room and incubator temperatures to different concentrations of glycerol

STRAIN OF TUBERCLE BACILLI	TEMPERATURE AT WHICH BACILLUS SUSPENSION IN GLYCEROL WAS KEPT	PERCENTAGE OF CONCENTRATION OF GLYCEROL	TIME OF EXPOSURE TO GLYCEROL			
			1 hour	3 hours	1 day	3 days
Gluckson	Room	25	++*	++	0	0
		50	+	+	0	0
		75	+	0	0	0
	Incubator	25	++	+	0	0
		50		0	0	0
		75		0	0	0
Human	Room	25	++	+	++	0
		50	++	0	+	0
		75	0	0	+	0
	Incubator	25	+		0	0
		50	+		0	0
		75	0		0	0
Bov. Vir	Room	25	+++	+++	+++	++
		50	+++	++	++	+
		75	++	++	+	0
	Incubator	25	+++	++	+	0
		50	++	++	0	0
		75	0	0	0	0
Bov. D	Room	25	+++	+++	++	++
		50	+	++	+	0
		75	0	0	0	0
	Incubator	25	+++	++	++	0
		50	++	0	0	0
		75	+	0	0	0

*The readings recorded are the average of 2 or 3 tubes seeded in each case. Readings were made after one and two months' incubation; only the two month average reading is recorded, however. The amount of growth on the medium is graded from 0 = no visible growth to +++ = a profuse, excellent growth.

of full strength, pure, sterile glycerol, making concentrations of 75, 50 and 25 per cent glycerol in saline solution, which were then well shaken and placed in the incubator and at room temperature (in a dark place). Seedii gs from these mixtures were made directly on to Petroff's

gentian violet-egg medium. After four and eight weeks' incubation the tubes were read. The findings are recorded in table 1.

Table 1 shows a greater susceptibility of the two human strains of tubercle bacillus to the different concentrations of glycerol than the two bovine strains. It is also to be noted that both types, human and bovine, of tubercle bacilli are more susceptible to glycerol at incubator than at room temperature. A choice of a satisfactory single concentration of glycerol and temperature of exposure left much to be desired in making a decision but it was finally arbitrarily decided to test the effect of 25 and 50 per cent glycerol at room temperature on ordinary tuberculous sputums containing the average run of contaminators,

TABLE 2

The effect of 25 and 50 per cent glycerol on the contaminators of tuberculous sputum

TUBERCULOUS SPUTUM	EXPOSURE AT ROOM TEMPERATURE IN HOURS								EXPOSURE TO 25 PER CENT GLYCEROL AT INCUBATOR TEMPERATURE IN HOURS			
	25 per cent glycerol				50 per cent glycerol							
	0.5	1	2	3	0.5	1	2	3	0.5	1	2	3
1	C*	C	C	C	C	C	C	C	C	C	C	?
2	C	C	C	C	C	C	C	C	C	C	C	C
3	C	C	C	C	?	C	C	C	C	C	C	C
4	C	C	C	C	C	C	C	C	C	C	C	C
5	C	C	C	C	C	C	C	C	C	C	C	C
6	C	C	C	C	C	C	C	C	C	C	C	C
7	C	C	C	C	C	C	C	?	C	C	C	C

* Definite and profuse growth of contaminators on the medium after keeping the culture tubes at incubator temperature for 5 days is indicated by "C" while a slight growth is indicated by "?".

and that of 25 per cent glycerol at incubator temperature on the same type of sputums. The times of exposure to glycerol were 0.5, 1, 2, and 3 hours after which the mixture was seeded on Petroff's gentian violet-egg medium. The results of testing seven different tuberculous sputums are recorded in table 2.

Table 2 reveals that neither a 25 and 50 per cent glycerol content of sputum, maintained for 3 hours at room temperature, nor 25 per cent glycerol content of sputum maintained for 3 hours at incubator temperature will destroy the contaminators present in tuberculous sputum.

The variability in the action of glycerol upon suspensions of different strains of tubercle bacilli and the inability to destroy contaminators

in concentrations, at suitable time intervals and suitable temperatures, at which glycerol is still innocuous to all strains of tubercle bacilli, would seem to preclude its use as a measure of cultivating tubercle bacilli from contaminated sources.

SUMMARY

Human and bovine tubercle bacilli are more susceptible to such high concentrations as 25 to 75 per cent of glycerol at incubator (37°C.) than at room (about 20°C.) temperature. The two human strains proved more susceptible to glycerol than the two bovine strains tested. Neither 25 and 50 per cent glycerol content of sputum maintained for 3 hours at room temperature nor 25 per cent glycerol content of sputum maintained for 3 hours at incubator temperature, the highest concentrations of glycerol and most suitable time interval of exposure found satisfactory to still preserve the viability of the tubercle bacilli for cultural purposes, was found capable of destroying the contaminators present in tuberculous sputum.

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THE REHABILITATION OF THE TUBERCULOUS EX-SERVICE MAN[1, 2]

WALTER C. KLOTZ[3]

The satisfactory reëstablishment in civil life of the men who served in the world war is still an enormous problem, and one of its most important phases is the man who has been disabled by tuberculosis. To appreciate fully the many difficulties that have been met in connection with this problem it would be necessary to give a detailed account of the various agencies of the government that have been successively engaged in its solution. It will be impossible to furnish in this place more than a general outline. It is especially important to point out that the question of tuberculosis as a war problem was considered from the beginning of hostilities and that very definite steps for the prevention and treatment of the disease had been taken early by the Army Medical Corps. At the same time, following the entrance of this country into the war, the National Tuberculosis Association became actively interested in the matter and in the rehabilitation of the tuberculous soldier. Through its executive officers it has, on numerous occasions, extended valuable aid and counsel to the government, while many of its members have at different times been actively engaged in various phases of this work.

That the subject should appeal to the members of our Association through a sense of patriotism and public service goes without saying. At the same time, it is of very practical significance to the tuberculosis specialist, industrial physician, public sanitarian or social worker. The estimated 40,000 cases of tuberculosis among former men in military service, taken from about 4,500,000 of our population, within about the same period, would represent valuable material for the study of data pertaining to questions of epidemiology, incidence and treatment of tuberculosis; while the questions of compensation, disability and industrial

[1] Read, in abstract, before the clinical section at the twentieth annual meeting of the National Tuberculosis Association, Atlanta, Georgia, May 7, 1924.

[2] Approved for publication by the President of the Board of Managers and the Chief Surgeon, National Home for Disabled Volunteer Soldiers.

[3] From the National Sanatorium (National Soldiers Home), Johnson City, Tennessee.

rehabilitation offer the elements of a very interesting problem in industrial hygiene, involving an occupation with special vocational hazard.

The rehabilitation problem has been discussed at former meetings of this Association, beginning with that held at Cincinnati in 1917. At that time we had just entered the war and had been filled with apprehension by the rumored prevalence of tuberculosis in the French army and among the French civilian population. It was ascertained later, through the work of Sergent and Rist, that the earlier reports of Landouzy and his dire forebodings had overestimated the tuberculosis situation and that many of the 86,000 men discharged from the French Army on account of tuberculosis were, upon subsequent examination, found to be suffering from other conditions. At the moment we realized that this menace to our own troops, about to be sent over-seas, might later assume serious proportions. At this same meeting it was accepted that all tuberculosis could not be eliminated entirely, and even at that early date we discussed the case of the soldier returning from over-seas with tuberculosis. We were told of some of their experiences by our Canadian confrères and were warned of some of their mistakes, mistakes that were made in the face of medical judgment as a result of popular opinion and sentiment. Later, we made these same mistakes and for the same reasons.

As far as prevention is concerned, we can say that we met the problem and that it was well met. The Surgeon General's office was fortunate in having attached to it Colonel George E. Bushnell, one of the most experienced tuberculosis specialists, who was placed in charge of the tuberculosis section of the Army Medical Corps. Through his efforts examinations for tuberculosis were instituted and a standard procedure for the diagnosis and rejection of recruits suffering from active or manifest tuberculosis were formulated, in the now famous *Circular No. 20.*

It would be interesting to recall more fully the work in connnection with these tuberculosis examinations, as they have a direct bearing on some of the phases of the present problem. Some of the diffculties, particularly the shortage of physicians experienced in tuberculosis work, were to be encountered again later, and the same measures to train such men were also subsequently employed in connection with the hospitalization problem. Bushnell has himself gone over this subject more recently (1). A few basic figures are mentioned here, as they will be referred to again below. The total number of tuberculosis examinations was 3,286,690. Of these 23,995 were rejected, or 7,204 per million. The

demobilization boards reported 1,356 cases of tuberculosis out of 2,566,200 examined, or 542 per million. It is noted, however, that all of these men had not been examined previous to service. The figures quoted are therefore subject to correction. But, even as they stand, they would indicate that, from a practical point of view, the army examinations did eliminate the greater number of those suffering from tuberculosis. It is only fair to state here also that Bushnell had never promised to eliminate all tuberculosis from the army. "The best we can hope for," he stated in 1917 (2), "is to keep the incidence of tuberculosis down to not more than two per thousand. A certain irreducible minimum will be inevitable." That this result was attained is a matter of record and, as far as the A. E. F. was concerned, tuberculosis never constituted a very large problem. There was a time during the epidemic of influenza in the fall of 1918 when large numbers of men were being sent back with a diagnosis of tuberculosis. But on reëxamination, after their arrival in this country, it was disclosed that a large proportion had been the subjects of wrong diagnosis.

However, the mobilization of this large army had hardly been completed when the war suddenly ended. Demobilization supervened and the new problem promptly merged with the old,—before the first was out of the way. With demobilization some of the postwar problems began to confront the country, a country that had staked its utmost efforts to win the war. Among these post-war problems were the reconstruction and readjustment of the disabled soldier and what concerns us especially, the soldier disabled by tuberculosis.

That certain plans and provisions to meet the problem of reëstablishment had been considered, has been mentioned. The War Risk Insurance Act provided that hospitalization and medical treatment should be furnished the disabled soldier. While no agency of the government was designated by that act it was properly assumed that the Army and Navy would furnish treatment for disabled men in their own hospitals. As a matter of fact, both of these departments had provided beds to meet this contingency. In the minds of those engaged in reconstruction, there seems to have been a very definite idea of keeping the men in the service, as would be indicated by an official bulletin issued by the Surgeon-General in 1918: "Hereafter no member of the military service, disabled in line of duty, even though not expected to return to duty, will be discharged from the service, until he has attained complete recovery or as complete recovery as it is expected he will attain when the nature of his

disability is considered" (3). The compensation provided for under the War Risk Insurance Act was obviously intended to take the place of the Army pay and was originally fixed at $30 per month for temporary total disability. It was felt that with such inducement men might remain in the service until they had been physically and industrially rehabilitated. In fact, the complete reëstablishment of the man was the essential purpose of the reconstruction plan. In order to supplement the work of the hospitals, the Rebahilitation Division of the Federal Board of Vocational Education was establised in June, 1918, in order to provide suitable training for those men whose disability constituted a vocational handicap. In discussing the reconstruction programme, Bushnell (4) comments on the advantages that would result through the fact that the men of the World War were not to be taken care of by means of the old Army pension plan and expressed the hope that influence would not be allowed to bring about their discharge until they had been fully rehabilitated. However, all these well-laid plans, which have been indicated here very briefly, were to a large extent defeated by circumstances which had not and could not be foreseen, circumstances which led to the very mistakes against which we had been warned.

With the signing of the armistice there was a marked psychological reaction against the war. The troops returning from over-seas, impatient at frequent delays in embarkation and transportation, had become resentful of anything military. Every man naturally wanted to return home, the disabled and the well, the man who needed care and treatment as well as the officers and men of the Medical Corps who were to have manned the service hospitals.

This feeling spread to the home. It was not long before every possible influence was brought to bear, and demobilization was speeded up. Soon there were insistent demands that men be discharged immediately. In some instances dying men were discharged and transferred home in the face of medical opinion, as a result of popular clamor. The plans for reconstruction and rehabilitation that had been so carefully worked out in 1917 and 1918 were disregarded.

It was but a short time before another reaction occurred when the needs for hospitalization became evident. The government was then forced to find some means of providing hospitalization and medical treatment, in accordance with its obligations, as formulated by the War Risk Insurance Act, virtually an employees' compensation law. But these men were now out of the Army and the Army was undergoing rapid

demobilization in response to popular opinion. Furthermore, the men did not want to go back to army hospitals. In response to these urgent demands the United States Public Health Service was assigned the task of providing hospitalization and medical treatment for the disabled and sick soldier by Act of March 3, 1919. With its twenty small marine hospitals, provided with less than 1,500 beds, with a limited commissioned personnel and practically no nursing corps, it set out to cope with a situation which in magnitude exceeded any calamity that had ever befallen this country. It was necessary to provide for a hospital programme immediately, which fulfilling its own predictions was to reach a peak of more than 30,000 in the next three years (5). In order to carry out such a programme, the Public Health Service was authorized to take over from the Army all hospitals and equipment not absolutely necessary for immediate use. These hospitals furnished about 9,000 beds. For operating expenses there was provided an appropriation of less than $10,000,000. The details of this period of the U. S. Public Health Service were covered by F. C. Smith in an address before the National Tuberculosis Association in 1921 (6).

The next two years, 1919 and 1920, witnessed those dark hours when the country remained apathetic and unresponsive to the repeated appeals of the Public Health Service for new, permanent and fireproof buildings with which to replace some of the temporary cantonment hospitals built hurriedly during the war, which even then were undergoing rapid deterioration and of which many were dangerous fire traps. Contracts were made with many civilian hospitals. In fact, the whole country was canvassed and a survey made of all possible facilities. Some of these contract institutions were satisfactory, others were inadequate or wholly unsuitable. Many of the contracts were soon cancelled. During 1920 arrangements were made to tide over the situation and help meet the emergency by expanding the facilities of the National Soldiers Home. The branch at Johnson City, Tennessee, with its splendid permanent structures was transformed into a modern tuberculosis sanatorium by the addition of sleeping porches. Similar arrangements at other branches provided for a total of 3,300 beds, while through like arrangements with the Army and Navy 3,270 beds were provided for disabled men of the World War.

The appeals of the Public Health Service were supplemented by the recommendations of the National Tuberculosis Association, the American Legion and other voluntary agencies, but it was not until the spring

of 1921 that the first Langley bill was passed and an appropriation of $18,000,000 made available. Of this amount $10,000,000 was allotted for tuberculosis hospitals. A hospitalization committee was appointed by the Secretary of the Treasury to prepare plans, locate sites and decide upon the equipment and operation of these additional hospitals. During the summer of 1921 the Veterans Bureau was created. This provided one bureau, directly under the President, to conduct the combined functions of the former Bureau of War Risk Insurance and Federal Board of Vocational Education. A year later, May, 1922, 57 of the hospitals operated by the U. S. Public Health Service were transferred to the Veterans Bureau, thus centralizing more the various activities under one head, although the U. S. Public Health Service has continued to assign commissioned officers for duty at these hospitals and retain control of the Marine Hospitals.[4] The beds in the National Soldiers Home, Army, Navy and Interior Departments have also continued under the administration of their respective departments or services.

As there have been much publicity and adverse criticism of the various government agencies, it is only fair to point out some of the difficulties and obstacles that had to be overcome by those who were responsible. Those who were present at the meeting of this Association held at New York in 1921 will recall the fearless and impressive address made by one of our former presidents, Doctor David R. Lyman (7), in which he analyzed so clearly and forcibly the limitations which existed at that time. As he put it, in speaking of the rehabilitation problem, "The limitations are so great as to make its successful solution under existing conditions appear almost impossible." It was at the time when the hospital peak of 1922 had not been reached and the hospital construction programme was just beginning to be developed. It was the moment when the morale of the men was at its lowest.

The men were embittered and discouraged by the long delays, delays that had best be laid at the door of a people and Congress, lethargic and inert, which could not be roused to the crying needs of the situation. It is not surprising, therefore, that the men were resentful toward the agencies and officers of the government, whom they held responsible for unfulfilled promises. It was on account of this wrong perspective that they were unwilling to coöperate with medical officers or conform to medical

[4] Legislation enacted by last Congress makes this transfer permanent and would discontinue assignment of commissioned officers from U. S. Public Health Service. It is provided that the Bureau establish its own medical personnel.

regulations. As Lyman stated at the time, there were men at the head of the various departments and services actuated by the highest ideals, but their efforts and intentions to help these men were frustrated by misapplied philanthropy and indiscriminating sentimentality, which permitted sick men to leave hospitals and return whenever they wanted, which permitted their transfer from one hospital to another as often as they demanded, and travel from one part of the country to another, under the mistaken notion that the change of climate would benefit them. Under the plea, "give this dying man a chance," many a patient was transferred to some distant point in the Southwest, depriving him of the small chance that he had, only to die at the point of destination or frequently even on the trains. Those who had the real interest of the man at heart and wanted to help him were helpless once more in the face of popular clamor or the raucous demands of the demagogue. The results were as disastrous as might have been expected. Fortunately the facts disclosed by Lyman and his co-workers, through their investigation, were so flagrant that some drastic action was finally taken and many of their recommendations have been carried out and are effective now.

It is perhaps futile and purposeless to go over these former shortcomings. The fact that there has been a succession of agencies assigned to this task might lead to the assumption that none of the preceding ones had been entirely satisfactory. But this repeated shifting of responsibility from one agency to another, for reasons as above outlined, had made efficiency all but impossible. Many of the difficulties have resulted from basic legislative acts, which had provided three different services to look after the same man at the same time. It was only to be expected that close coördination of the subordinate personnel of these three different services would be difficult, no matter how loyally and faithfully the heads of these different services might want to coöperate. It was impossible to carry out a unified plan of operation with the Bureau of War Risk Insurance determining eligibility for hospitalization and compensation, the Army or the Public Health Service furnishing this hospitalization and the Federal Board attempting to rehabilitate the same man industrially.

The development of these basic legislative acts by successive amendments offers a very interesting study, but time prevents all but a brief consideration of the provisions that affect the ex-service man disabled by tuberculosis. One of these amendments provided that a man passed by a draft board or one who volunteered for service, who was subsequently

rejected by a tuberculosis examining board, would be entitled to all benefits under the War Risk Insurance Act. This ruling has determined quite a group who saw no actual service, who were properly eliminated by the tuberculosis examinations, and are included among the 23,995 rejected, but who are eligible for compensation and medical treatment. How many of these are among the active claims on file would require a very laborious search of records. The second series of amendments are those that have gradually increased the interval following discharge, within which tuberculosis becoming manifest shall be considered "in line of duty" or "of service origin." At one time ninety days, this has been extended successively to three years. In other words, if tuberculosis develops within three years after discharge, the man is entitled to full disability compensation and hospitalization, to the point of physical rehabilitation or "arrest," with allowance for dependents.[5]

In May, 1923, there were about 41,000 active claims for tuberculosis on file. According to the above provisions, therefore, these men would fall into three groups: (1) those discharged S. C. D. within 60 days of induction into service, (2) those who were discharged more than 60 days after induction into the service and (3) those who were discharged without disability and who developed tuberculosis at varying periods after separation from the service. To determine this distribution for the present effective strength of the Veterans Bureau would be an almost impossible task. However, a group of 1000 men treated at the National Sanatorium, Johnson City, Tennessee, would probably represent fairly average conditions. Among these men discharged during the year 1923, fifteen had been discharged S. C. D. less than 60 days after induction into the service, 105 more than 60 days after induction and 880 had been discharged without disability, but developed tuberculosis after discharge, as follows: 538 less than two years after discharge and 342 more than two years after discharge. In one district in which the military population was 253,000 there were on file 4,100 cases of tuberculosis. This included some Southern States in which, on account of the colored population, the rate is relatively high. It would be difficult to accept any figures as accurate. Most of these men belonged to the age period of greatest incidence of tuberculosis and, with the more liberal extension of benefits, the number of claims would probably exceed the figures for known tuberculosis among

[5] In accordance with law enacted by last Congress this interval has been increased to January 1, 1925.

the civilian population. This is all the more true because, in addition to hospitalization and treatment, there is the provision of compensation. In other words, there is a very definite inducement held out to the man to have tuberculosis discovered. The existing figures therefore are of little significance as far as any relation to military service is concerned. They might represent a fairly complete tuberculosis survey of the men accepted for service, if it were not for the very large probable percentage of error in diagnosis. Moreover, where there was the responsibility, involving financial consideration and the effect of frequent criticisms, there would be a tendency to give the man the benefit of the doubt, in order not to arouse antagonism and further appeals. In the rehabilitation work, as in the case of the tuberculosis examinations of the army, there has been a definite scarcity of properly trained tuberculosis physicians; and it has long been established that the less-experienced man is more prone to make a diagnosis of tuberculosis on insufficient grounds than the one more experienced, who being more sure of himself is willing to back up his medical opinion fearlessly, in spite of any possible criticism. Many of our preconceived notions gained through civilian tuberculosis work have undergone definite change. Even in connection with the clinical history it has been found necessary to change our procedure. Many of these men have heard the symptoms repeated so often in other hospitals that they have come to believe that they are really suffering from them, although their statements may be made sincerely and honestly.

Owing to this lack of sufficient physicians with experience in tuberculosis, it was necessary in the beginning to train many new medical men. It has taken time therefore to organize medical work and to establish adequate standards for diagnosis and treatment. With more thorough examination on admission and readmission, we have come to suspect that there has been a considerable percentage of error in diagnosis in the past. It will be recalled that many men were sent home from the A. E. F. with a mistaken diagnosis of tuberculosis and that this was especially true during the influenza epidemic of 1918. Similar errors in diagnosis have been reported in connection with the allied armies as well as those of the Central Powers, both during the war and since then. The importance of differentiating pulmonary tuberculosis from nontuberculous pulmonary affections has been emphasized frequently during recent years. Postinfluenzal conditions have caused us to revise many preconceived clinical ideas. With such reports from various sources showing a high

percentage of error, we have come to analyze our examination findings more critically. Excessive tendency on the part of recently trained medical officers to rely upon X-ray interpretation, without proper correlation of physical examination and other clinical findings, may have been a source of such errors in the past. The importance of sputum examinations has been strongly emphasized. But, in spite of rigid and thorough laboratory technique and repeated direct examinations and use of concentration methods, and with strict insistence on careful and prolonged search of slides, the percentage of positive sputum cases has not exceeded 25 per cent of the average hospital population. It has been found necessary, moreover, to have all specimens of sputum certified to prevent fraudulent substitution.

One other very frequent source of error has been the presumptive diagnosis of tuberculosis in cases of infection of the upper air passages. Many such cases, diagnosed as tuberculosis on former admissions, clear up under appropriate treatment for sinus disease, infected tonsils, carious teeth and other forms of focal infection.

On account of financial considerations mentioned and the frequent criticism of government agencies, it is difficult to eliminate such presumptive tuberculosis or to refuse hospitalization. With financial benefit provided by the government in the form of compensation, at the basic rate of $80 per month, it is to be expected that a group of men would exist who are anxious to have a diagnosis of tuberculosis established. It requires some strength of mind and honesty of purpose, therefore, to make a negative diagnosis under such circumstances, even if no evidence of tuberculosis can be discovered after careful observation.

In connection with treatment we may confess certain limitations. There is still a scarcity of physicians who are experienced in the sanatorium management of tuberculosis patients. It is feasible, by intensive instruction, to train medical men in making satisfactory chest examinations, but it is a matter of years to train physicians so that they will understand tuberculosis in its broader clinical, psychological, sociological and economic aspects. There has always been a scarcity of such kinds of men and civilian tuberculosis activities have absorbed them. On the other hand, there are a number of reasons why such kinds of men have not been attracted more to those government services that were expanded to meet the exigencies of the rehabilitation programme. The greatest deterrents have been the lack of coöperation on the part of the patients and the interference with remedial measures through nonmedical or nonofficial sources.

It has been especially in connection with ambulant patients that the greatest limitation has been felt. The men who feel perfectly well cannot see the need of medical restrictions and control. To them such measures recall the routine of military regulations. It is in the care and management of ambulant groups that the best-trained men are needed; physicians who through their personal force, tact and sympathy can inspire their patients with the belief that the doctor knows what is best for them and that he really wants to help them. If such patients are given little more than domiciliary care they will fail to see the medical significance of sanatorium rules and regulations. We must do more to keep their future in view and to visualize in advance by what means we can help them most to become reëstablished, both physically and industrially. If, in the treatment of tuberculosis medical service is limited to medication, we cannot blame the patient if he fails to appreciate the need for further hospitalization or sanatorium treatment.

As far as results of treatment are concerned, we are not in a position with existing figures at our disposal to make even approximate estimates as to the percentages of permanent arrest or complete rehabilitation. With many men leaving hospitals "A. W. O. L." or "Against Medical Advice," with frequent readmissions, transfers, passes and furloughs, it is not reasonable to expect as good results as are obtained in the better class of civilian institutions, where closer medical supervision and stricter discipline can be maintained. On the other hand, it is only fair to state that among patients in government tuberculosis hospitals there are men who want to get well and who have followed treatment conscientiously and faithfully without interruption for several years. The reports of the Veterans Bureau for the fiscal year ending June 30, 1923, (8) showed the status on discharge of a total of 25,412 cases of tuberculosis. These figures are shown in table 1. They are subject to proper interpretation, as the number of "cases" does not represent individual "patients." The same patients are probably included in the statistics of several hospitals in the course of the same fiscal year, having been discharged and readmitted to different institutions successively. This is probably all the more true as these statistics apply to Bureau beneficiaries discharged from "all hospitals," including those of the Public Health Service or Veterans Bureau as well as those of the Army, Navy, Soldiers Home, State and private civilian contract hospitals. With the various agencies engaged in the problem and the decentralization of records, it would be an almost superhuman task to make a satisfactory study and analysis

TABLE 1

Disposition or status on discharge, Veterans Bureau Beneficiaries, classified "Pulmonary Tuberculosis," discharged from all hospitals, during the fiscal year, ending June 30, 1923. This refers to number of cases and not necessarily to number of individual patients, as the same patient may affect statistics for several hospitals during the same fiscal year on account of transfer or readmission after discharge from another hospital. Compiled and consolidated from tabulated statistics. Annual Report, Director, U. S. Veterans Bureau, for year ending June 30, 1923, Gov. Printing Office, Washington, D. C., 1923.

DISPOSITION ON DISCHARGE	JULY	AUGUST	SEPTEMBER	OCTOBER	NOVEMBER	DECEMBER	JANUARY	FEBRUARY	MARCH	APRIL	MAY	JUNE	TOTAL
Cured or restored	4	2	3	0	4	1	1	1	0	1	0	1	18
Improved or apparently arrested	544	536	567	519	426	455	402	448	464	513	529	330	5,733
Unimproved, maximum benefit	139	136	112	83	71	61	95	76	102	111	102	68	1,156
Transferred to home treatment	66	82	69	67	76	85	74	42	69	97	128	78	933
Transferred to other hospitals	251	293	256	305	350	228	237	270	274	221	458	309	3,452
Died	147	124	122	122	133	155	154	168	150	162	134	106	1,677
Discharged against medical advice	377	365	459	362	292	254	249	247	304	350	383	260	3,902
Left without permission	319	327	325	284	283	281	274	267	273	313	319	247	3,512
For disciplinary reasons	75	89	59	55	43	43	50	55	42	38	48	22	619
No tuberculosis treatment, not indicated	380	423	466	459	479	409	365	272	348	303	333	173	4,410
Total	2,302	2,377	2,438	2,256	2,157	1,972	1,901	1,846	2,026	2,109	2,434	1,594	25,412

Note: The use of term "cured" is taken without explanation. No differentiation was made in annual report between "improved" and "apparently arrested."

of the statistics now obtainable, leaving out of consideration the probable percentage of error in the functions which enter into their calculation. For the purpose of obtaining more definite figures, we have taken a group of 1,544 patients discharged from the National Sanatorium, Johnson City, Tennessee, during the year ending December 31, 1923, and the results are shown in table 2.

However, the important question is, "What becomes of the man after he leaves the hospital?" It is in connection with this question that there appears to be the greatest need at the present time. To keep

TABLE 2

Status on discharge of patients discharged from the National Soldiers Home, Mountain Branch (National Sanatorium), Johnson City, Tennessee, during the twelve months ending December 31, 1923

DISPOSITION ON DISCHARGE	JANUARY	FEBRUARY	MARCH	APRIL	MAY	JUNE	JULY	AUGUST	SEPTEMBER	OCTOBER	NOVEMBER	DECEMBER	TOTAL
Apparently arrested	16	20	24	18	25	10	35	27	38	30	56	43	342
Transferred to home treatment	1	4	3	1	4	1	2	3	3	2	4	2	30
Transferred to other hospitals	7	8	5	4	6	3	6	9	13	25	7	6	99
Died	6	10	11	4	6	4	7	10	3	3	0	2	66
Discharged against medical advice	31	31	33	33	30	33	45	26	37	26	9	17	351
Left without permission (A. W. O. L.)	25	27	40	69	58	58	55	71	51	58	39	32	583
Discharged for disciplinary reasons	2	3	4	4	7	6	9	0	5	2	2	6	50
No indication for treatment	2	1	1	1	2	3	2	2	3	1	3	2	23
Total	90	104	121	134	138	118	161	148	153	147	120	110	1,544

Note: Among the groups discharged "Against Medical Advice," "A. W. O. L." and "Disciplinary Reasons," would be included some who had improved and some who had not improved. For the sake of clarity no attempt has been made to make such a subdivision on clinical grounds. The object of this tabulation was to show the administrative reasons governing discharges.

these men in a hospital or sanatorium indefinitely is not wise. But some form of machinery is needed for the postsanatorium readjustment period. There lies the greatest gap in the present scheme of organization. To stop with discharge is to omit one of the most important phases in the whole rehabilitation programme. Medical supervision and follow-up of some kind should be continued for a varying period. This should be correlated closely with the hospital where the patient has been treated. For some this readjustment period will be temporary, for others it will be indefinite, while for the group in which there is no hope for rehabilita-

tion it will be permanent. For the first two groups some form of occupation is essential. Idleness is the most prolific source of relapse and retrogression.

Lack of closer correlation between the medical service and the rehabilitation division has caused too great a distinction between physical rehabilitation and industrial reëstablishment. As a consequence of this lack of correlation, the patient passes entirely from under observation and control of the doctor who may have treated him for many months, who knows all the details of his individual case and who knows in what manner he reacts to exercise, work and fatigue. Through lack of such medical supervision after discharge, the man frequently breaks down again and must be rehospitalized. In other instances a less experienced field examiner, seeing the patient for the first time, becomes alarmed at some stray râle. He sends him back to the hospital, in order, as he thinks, to give the patient the benefit of the doubt. But it is a very grave question whether it is really giving any patient the benefit of the doubt to relabel him "active tuberculosis" and to subject him to further hospitalization needlessly, to defer rehabilitation indefinitely and to cause the patient new discouragement.

As mentioned above, the complete physical and industrial reëstablishment was the end-result aimed at. By an Act of June, 1918, there had been created the Rehabilitation Division of the Federal Board of Vocational Education. This new division was charged with the industrial rehabilitation of the man who had suffered vocational handicap as a result of disability. The Federal Board originally created by an Act of February, 1917, to supplement the work of the Federal Workingmen's Compensation Act, had developed its activities largely to meet the handicaps resulting from industrial accidents and injuries. One important provision was that in the case of the handicapped disabled ex-service man, compensation or "training pay" should be furnished by the government, during the period of training in addition to dependency allowances.

Some phases of this reconstruction work were at first carried out in various hospitals. Later separate training centres were established in order to remove the trainee proper from the hospital. However, a great deal of the training was arranged for through various technical schools, colleges and universities, and especially through the system of replacement training, a species of apprenticeship. It can readily be conceived by the tuberculosis worker, that to put the man discharged as

apparently arrested to work, on full-time basis, without medical supervision, without careful gradation of work and without careful observation and control as to relapse, would not be expected to bring about satisfactory results.

The above-mentioned training centres, such as the one at Waynesville, North Carolina, Pascagoula, Mississippi, and Pocono Pines, Pennsylvania, should have offered excellent opportunities for developing some of the postsanatorium treatment and training that tuberculosis workers have found such a vexing problem for many years. If vocational training in cases of tuberculosis had from the beginning been guided more by the medical indications, more permanent results might have been obtained. With the removal of the vocational or reconstruction work from the hospitals, the work in the hospitals became limited to occupational therapy, which was placed under medical supervision. While this change insured the regulation of therapeutic exercise along medical lines, in the sense of diversion, mental occupation and physical reconstruction, it has perhaps caused prevocational and vocational training, with complete physical and industrial rehabilitation, to become too remote. In other words, the real purpose of treatment has to a certain degree been forgotten. During the period that the "Rehabilitation Division" was still operating in the hospitals, the question of vocational training and future plans would be discussed with the man during his convalescence and, in order to save time, this period was often used to begin some prevocational training. In this way the man was perhaps often rushed through too fast and his ambition roused beyond his physical strength, to be followed soon by relapse and discouragement. However, another difficulty has been engendered, since all correlation has been lost between hospital and medical treatment on the one hand and vocational training on the other; especially when training is not carried out at a training centre and the man is not under any medical supervision or protection. As a result of this lack of coördination, it has happened in only too many instances that the man discharged from the hospital is allowed to overdo, placed in a position of having to compete with the student or worker who is not physically handicapped and is sooner or later obliged to return to the hospital for further treatment on account of relapse. We are not surprised that it does happen. We would be more surprised if it did not occur, as long as the medical aspects of the postsanatorium, tuberculous patient are disregarded.

In a retrospect of the rehabilitation work so far we cannot but see the many difficulties that have arisen and the many obstacles that have lain in the way. Those who have been officially responsible have been hampered by circumstances beyond their control. Many of the limitations pointed out by Lyman in 1921 have been removed. Some of the recommendations made in his address have been carried out. The hospital-construction programme is now nearly completed. One very important point brought out by Lyman was the lack of coöperation on the part of the men themselves. Conditions in this respect have improved. General Order Number 27 and its amendments have helped to solve many difficulties that the medical staff and nursing personnel were called upon to meet during the earlier period.

For the final step in the problem, reëstablishment, both physical and industrial, it is by no means easy to offer any definite solution. The "try-out" training centres, with more intensive medical supervision and greater consideration of the physical aspects, would come nearest to fulfilling the requirements of sheltered employment, together with graded work and industrial training along practical lines. Such training centres might well be multiplied and placed in close proximity to existing hospitals, in order that patients might report for periodic examinations to the physician who had treated them and who would be familiar with their cases.

Administration and overhead expense would obviously be reduced by a straight pension system, with optional hospitalization. But, as may be recalled, those who planned the reconstruction programme when we entered the war wanted to avoid the old pension system, because they believed it would defeat rehabilitation. The economic advantages should not determine the question from the medical and sociological aspects. If we are still anxious to save these men to themselves, to their families and to our country, further efforts must be continued along lines similar to those now projected. But better means should be provided for medical service during the postsanatorium readjustment period. Adequate compensation should be continued to the point of complete rehabilitation, even without vocational training, provided the man is making efforts to become reëstablished. If vocational training is continued it should be more carefully graded. It should be under more careful medical supervision. There should be greater consideration of medical aspects and of physical rehabilitation in the choice of employment. Medical supervision should not be limited to the amount and

grade of work, but should exercise reasonable and sensible control as to mode of living, housing and hygienic environment, in the same manner as is now being done in connection with many university students.

We have seen how, in the beginning of this work, various influences have interfered from time to time with the best interests of the man whom we are trying to help; how various cross currents, such as misplaced philanthropy added to those of selfish interest, have kept him in a constant state of restlessness and discontent. We have seen how the lure of compensation has come to mean more to some than the restoration of health. It is important, therefore, to be on our guard, lest popular clamor, not knowing the facts, or the agitation of the demagogue, actuated by self-interest, may again lead to serious mistakes and defeat our efforts to complete the rehabilitation of the veteran disabled by tuberculosis.

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A STUDY OF READMISSION AND RELAPSE OF TUBERCULOSIS PATIENTS[1,2]

IN 200 CONSECUTIVE CASES OF EX-SERVICE MEN READMITTED TO THE NOVA SCOTIA SANATORIUM

A. F. MILLER

At the Nova Scotia Sanatorium, we made, during 1921 and 1922, a special study of readmissions, 200 consecutive cases of ex-service patients. From the statistics so gathered and from our experience with these patients, we have drawn some conclusions which may be of interest to those who are trying to care for and reëstablish the tuberculous ex-service man and, indeed, for other tuberculosis workers as well.

Our experience with ex-service men covers the period since 1916; in fact, we had a few as civilian patients in 1914 and 1915. Up to 1916 ours was a Provincial Government institution for tuberculous civilians only. In 1917 the Dominion (Federal) Government's Military Hospitals Commission entered into an arrangement by which they erected buildings here for the accommodation of 300 of their tuberculous patients. Later these patients became the protégés of the Dominion Department of Soldiers' Civil Reëstablishment while undergoing treatment and of the Board of Pension Commissioners of Canada after their discharge from the Sanatorium. This system still continues, and the Board of Pensions, bringing each man up for reëxamination every six months while he is receiving pension, usually refers its tuberculosis patients and suspects to us, especially those who have been treated at our institution; and, their eligibility for treatment and pension having been established on the ground that military service has actually caused or aggravated the disease, their pension is regulated or re-treatment recommended largely upon our findings. Consequently, our examinations have to be most thorough, using every facility and aid to diagnosis; and we keep these men from ten to fourteen days for observation and study, and in dubious cases a month or more.

[1] From the Nova Scotia Sanatorium for Tuberculosis, Kentville, Nova Scotia.

[2] Read, in abstract, before the Conference of Medical Superintendents of the Department of Soldiers Civil Reëstablishment Sanatoria, Ottawa, Canada, April 8, 1924.

In all, 1338 ex-service patients have been admitted to and treated at the Nova Scotia Sanatorium, and 430 have been readmitted, many of them several times. This has afforded us an unusual opportunity of checking up our examination findings and of following up the post-discharge history of military patients over a period of seven years.

It is obvious that from the economic standpoint there are differences between the post-discharge condition of these men and that of our civilian patients. Civilian patients cannot usually afford the extended period of sanatorium treatment necessary to a good arrest of their disease, few remaining longer than six months; and civilians have no government support for themselves or their families during the post-discharge period and no regular examinations after discharge. They have to keep up their health as best they can and make a living, more or less, or depend upon their families. The military patient, for an indefinite period following the completion of sanatorium treatment, may report to a Department of S.C.R. physician when suffering from reactivation of symptoms, and in such cases he is readmitted to the sanatorium for observation and treatment if necessary.

As to our examinations, the standard is about the same as that of other sanatoria in good standing. They include (1) a history of the present illness, especially in its bearing upon army service, for the reason that one year after discharge from the Forces the man is not entitled to treatment unless there is documentary proof of a former disability; (2) in readmission cases, a history of the patient since his discharge from the sanatorium with special bearing upon the causes of relapse; (3) complete physical examination; (4) nose and throat examination; (5) dental examination; (6) laboratory tests (sputum, complement fixation, Wassermann); (7) X-ray examination, fluoroscopic and stereoscopic; and (8) in readmissions, comparison of former X-ray plates and physical findings with the present ones.

In every case in which sputum is negative for tubercle bacilli on examination by the usual direct-smear method, the concentration method is tried.

All the examination reports in each case are brought up at our weekly meetings of the medical staff, when findings are correlated and diagnosis decided upon.

In the present study of 200 readmissions we have attempted to divide them into *Relapsed* and *Not Relapsed*, but such a classification cannot be made of hard and fast precision, as a considerable number of chronic

cases have to be included in which the patient had some active disease on discharge from the sanatorium, and naturally the disease continued to extend while he took the cure at home. We have, in this study, placed in the *Relapse* group all patients who showed either extension or

TABLE 1

The number who had *Relapse* was	66 or 33 per cent
The number who had *No Relapse* was	134 or 67 per cent

activity of their disease, or both, on readmission. How many were genuine relapses may be learned from the *Comparison of Conditions*, tables 5 and 6.

The pulmonary condition on first admission is given in the following table, the two groups, for the purpose of comparison, being separated:

TABLE 2

	CONDITION ON ADMISSION						
	Not tuberculous	Suspected tuberculosis	Minimal	Moderately advanced	Far advanced	Non pulmonary tuberculosis	Total
Relapse		3	3	40	20		66
No relapse	35	11	45	39	3	1	134
Totals	35 or 17.5%	14 or 7%	48 or 24%	79 or 39.5%	23 or 11.5%	1 or 0.5%	200 or 100%

It will be noticed that of the 35 who were diagnosed as not tuberculous on admission none relapsed; of the 14 suspects 3 or 21.5 per cent relapsed; of the 48 minimal 3 or 6.2 per cent relapsed; of the 79 moderately advanced 40 or 50.6 per cent relapsed; and of the 23 far advanced 20 or 86.9 per cent relapsed.

The diagnosis in the 35 not tuberculous cases will appear in table 3.

Of the 151 definitely tuberculous on admission the condition on first discharge from the sanatorium is shown in table 4.

For a detailed comparison of the different groups, as to condition on admission, on discharge and on readmission, see tables 5 and 6.

Of the 3 suspected who relapsed, table 5 shows that the 2 who were discharged improved came back, 1 minimal, active, and 1 moderately advanced, active. One who was diagnosed nontuberculous on discharge came back far advanced, active. This man had been away from our observation for over two years.

TABLE 3

Diagnosis on admission in the not tuberculous cases

Chronic Bronchitis	18 or	51.4 per cent
Trauma of Chest	4 or	11.4 per cent
Debility	4 or	11.4 per cent
Pneumonokoniosis	2 or	5.7 per cent
Bronchial asthma	1 or	2.8 per cent
Mitral disease	1 or	2.9 per cent
Exophthalmic goitre	1 or	2.9 per cent
Syphilis	1 or	2.9 per cent
Dementia praecox	1 or	2.9 per cent
No Disease	2 or	5.7 per cent
Total	35 or	100 per cent

TABLE 4

Condition on discharge of the definitely tuberculous

Apparently cured	1 or	0.7 per cent
Arrested	28 or	18.6 per cent
Apparently arrested	30 or	19.8 per cent
Quiescent	52 or	34.4 per cent
Improved	24 or	15.9 per cent
Unimproved	16 or	10.6 per cent
Total	151 or	100 per cent

TABLE 5

Analysis of relapse cases, showing condition on admission, discharge and readmission

CONDITION ON ADMISSION	CONDITION AT DISCHARGE	CONDITION ON READMISSION			TOTALS
		Minimal active	Moderately advanced active	Far advanced active	
Suspected tuberculosis (3)	Improved	1	1		2
	Nontuberculous			1	1
Minimal (3)	Apparently arrested	2	1		3
Moderately advanced (40)	Arrested		10		10
	Quiescent		10	9	19
	Improved		4	3	7
	Unimproved		1	3	4
Far advanced (20)	Quiescent			8	8
	Improved			2	2
	Unimproved			10	10
Totals		3 or 4.6%	27 or 40.9%	36 or 54.5%	66 or 100%

Of the 11 suspected who did not relapse, table 6 shows that all were discharged as improved, 7 were diagnosed as nontuberculous on readmission and 4 as still doubtful.

Of the 3 minimal who relapsed, table 5 shows that all were apparently arrested on discharge, 2 came back minimal, active, and 1 moderately advanced, active.

TABLE 6

Analysis of no relapse cases (134) showing condition on admission, discharge and readmission

CONDITION ON ADMISSION	CONDITION ON DISCHARGE	CONDITION ON READMISSION						TOTAL
		Not tuberculous	Suspected tuberculosis	Apparently cured	Arrested	Quiescent	Nonpulmonary	
Nontuberculous (35)	Improved	34						34
	Unimproved	1						1
Suspected tuberculosis (11)	Improved	7	4					11
Minimal (45)	Apparently cured			1				1
	Arrested or apparently arrested			17	10			27
	Quiescent			3	1	3		7
	Improved			8		2		10
Moderately advanced (39)	Arrested or apparently arrested			12	6			18
	Quiescent			5		10		15
	Improved			1		3		4
	Unimproved			1	1			2
Far advanced (3)	Quiescent					3		3
Nonpulmonary tuberculosis (1)	Improved						1	1
Totals		42 or 31.4%	4 or 2.9%	48 or 35.8%	18 or 13.4%	21 or 15.8%	1 or 0.7%	134 or 100%

Of the 45 minimal who did not relapse, table 6 shows that the 1 who was apparently cured at discharge came back apparently cured; the 27 who were arrested or apparently arrested at discharge came back, 17 apparently cured, 10 arrested; of the 7 whose disease was quiescent at

discharge, 3 were apparently cured, 1 arrested and 3 quiescent on readmission; of the 10 who were improved at discharge, 8 were apparently cured and 2 quiescent on readmission.

Of the 40 moderately advanced who relapsed, table 5 shows 10 arrested at discharge, all of whom were moderately advanced, active, on readmission; 19 quiescent at discharge, 10 of whom were moderately advanced, active, and 9 far advanced, active, on readmission. Of the 7 improved at discharge, 4 were moderately advanced, active, and 3 far advanced, active, on readmission.

Of the 39 moderately advanced who did not relapse, table 6 shows that 18 were arrested at discharge, 12 of whom were apparently cured and 6

TABLE 7

Not tuberculous	42 or	21.0 per cent
Nonpulmonary tuberculosis	1 or	0.5 per cent
Suspected tuberculosis	4 or	2.0 per cent
Pulmonary tuberculosis:		
Minimal, apparently cured	29 or	14.5 per cent
Minimal, arrested	11 or	5.5 per cent
Minimal, quiescent	5 or	2.5 per cent
Minimal, active	3 or	1.5 per cent
Moderately advanced, apparently cured	19 or	9.5 per cent
Moderately advanced, arrested	7 or	3.5 per cent
Moderately advanced, quiescent	13 or	6.5 per cent
Moderately advanced, active	27 or	13.5 per cent
Far advanced, quiescent	3 or	1.5 per cent
Far advanced, active	36 or	18.0 per cent
Total	200 or	100.0 per cent

arrested on readmission; of 15 quiescent at discharge 5 were apparently cured and 10 quiescent on readmission; of 4 improved at discharge 1 was apparently cured and 3 quiescent on readmission; of 2 unimproved at discharge 1 was apparently cured and 1 arrested on readmission.

Of the 20 far advanced who relapsed, the 8 who were quiescent at discharge, the 2 who were improved at discharge and the 10 who were unimproved, all were far advanced, active, on readmission. Naturally, there are comparatively few *No Relapse* in this class, only 3 having been discharged as quiescent and found still quiescent on readmission.

It will be seen, then, that in our 200 cases the readmission condition was as shown in table 7.

It might be supposed that the length of time spent at the sanatorium during the first treatment would have some direct bearing upon the

incidence of relapse among discharged patients. That is, patients who can remain under treatment long enough to get their disease well in hand would have a better chance of maintaining their health after discharge. Military patients, however, do not leave the sanatorium until treatment is completed unless they so desire. Consequently, in table 7 it is seen that there is, if anything, an inverse relation between length of treatment and probability of relapse, those who received 1 to 3 months' treatment showing 18.8 per cent of relapse while in those who had spent 3 to 6 months at the sanatorium the percentage of relapse is 20.5 per cent; 6 to 12 months, 40.6 per cent; 12 to 24 months, 47.6 per cent; over 24 months, 100 per cent. This is explained by the fact that the military patient who has most serious disease remains at the institution, as a rule, longer than the less seriously affected; in short, the period of treatment is usually in direct proportion to the amount of tuberculous trouble present. And naturally, the more trouble a man has, the greater is his liability to relapse (table 8).

The same reasoning applies to the relation between relapse and the length of time the patient was away from the sanatorium (table 9).

The length of time patients were kept on at the sanatorium after readmission is shown in table 10.

It may be surprising that so many were readmitted without evident or clinical disease, and we may note that 39 of those in the present study were kept at the sanatorium only for the 2 weeks' period of observation. In some cases, moreover, in which there has been no definite relapse, it is considered advisable as a preventive measure to keep the patient for a period of treatment. Further, several of the nontuberculous group who suffer from chronic bronchitis are undoubtedly in need of treatment at times, and, though their improvement is usually only temporary, it has been expedient in some of these cases to keep the patient at the sanatorium for a couple of months, especially when his home conditions, climate, etc., seem to warrant it. We believe, however, that most of these patients might do as well at home, with periodic care and rest, as they can under the costly treatment at a sanatorium.

Study of the histories in these readmission cases, that is, the history of the period since discharge from the sanatorium, is interesting from two points of view, the medical and the economic; and necessarily the one bears upon the other.

It is notable that the medical history, that is, the symptoms, are misleading, in that many of the symptoms formerly and usually regarded

as distinctly indicative or suggestive of tuberculosis are almost universally present, even in nontuberculous and in well-arrested cases. One hundred and eighty, or 90 per cent, of our 200 gave three or more

TABLE 8

Comparison of relapse and no relapse cases with regard to duration of first treatment at the sanatorium

	LESS THAN 1 MONTH	MONTHS 1–3	MONTHS 3–6	MONTHS 6–12	MONTHS 12–24	MONTHS 24–36	TOTALS
Relapse	1 or 9.1%	6 or 18.8%	9 or 20.5%	28 or 40.6%	20 or 47.6%	2 or 100%	66 or 33%
No relapse	10 or 90.9%	26 or 81.2%	35 or 79.5%	41 or 59.4%	22 or 52.4%		134 or 67%
Totals	11 or 100%	32 or 100%	44 or 100%	69 or 100%	42 or 100%	2 or 100%	200 or 100%

TABLE 9

Length of time away from sanatorium

	MONTHS 1–3	MONTHS 3–6	MONTHS 6–12	MONTHS 12–24	MONTHS 24–36	MONTHS 36–48	MONTHS OVER 48	TOTALS
Relapse	1 or 25%	9 or 40.9%	17 or 27.4%	21 or 42.8%	12 or 35.3%	4 or 18.2%	2 or 28.6%	66 or 33%
No relapse	3 or 75%	13 or 59.1%	45 or 72.6%	28 or 57.2%	22 or 64.7%	18 or 81.8%	5 or 71.4%	134 or 67%
Totals	4 or 100%	22 or 100%	62 or 100%	49 or 100%	34 or 100%	22 or 100%	7 or 100%	200 or 100%

TABLE 10

Duration of treatment after readmission (200 cases) (that is, the one period following that readmission covered by history)

OBSERVATION ONLY	MONTHS 1	MONTHS 2	MONTHS 3	MONTHS 4	MONTHS 5	MONTHS 6	MONTHS 7–12	MONTHS 12 OR OVER	TOTAL
13 or 19.5%	18 or 9%	16 or 8%	12 or 6%	16 or 8%	14 or 7%	15 or 7.5%	37 or 18.5%	33 or 16.5%	200 or 100%

of these symptoms (usually cough, expectoration, pains in the chest and weakness). One hundred and seventeen, or 58.5 per cent, gave what might be called a positive history. The incidence of symptoms is shown in table 11.

In the 35 nontuberculous cases the symptoms given were cough in 30 or 85.7 per cent, expectoration in 29 or 82.9 per cent, pains in the chest in 34 or 97.1 per cent, haemoptysis in 6 or 17.1 per cent, fever in 10 or 28.6 per cent, loss of strength in 31 or 88.6 per cent and loss of weight in 32 or 91.4 per cent.

In many of these the symptoms were genuine and due to respiratory diseases other than tuberculosis, such as chronic bronchitis, bronchiectasis, bronchitis caused by poison gas, bronchial asthma, anthracosis, rhinopharyngeal disease, etc.

In some cases the presence and persistence of symptoms not accounted for by any medical findings may be explained on the ground of a form of war neurosis, partly due to hospitalization and to the patient's peculiar reaction to the word "tuberculosis," which has been applied to him at some time in his medical history. There is a deepseated element of

TABLE 11

Symptoms present in 200 readmission cases

Cough	178 or 89.0 per cent
Expectoration	169 or 84.5 per cent
Pains in chest	169 or 84.5 per cent
Loss of weight	169 or 84.5 per cent
Loss of strength	161 or 80.5 per cent
Rise of temperature	88 or 44.0 per cent
Haemoptysis	39 or 19.5 per cent

dependence and inertia in human nature and, when it gets a chance to develop, it results in loss of moral "tone," of the sense of responsibility, the desire to achieve, to be independent, to excel. And we must remember that, when a man has but little education and no technical training, and can look forward to nothing but labor as a means of earning a living, a physical disability leaves him with no chance at all in the world of labor competition. It is no great wonder that the thought of ill health overcomes such a man and tends to make him afraid. The only way to overcome this fear, or, shall I say, to cure this neurosis, is to have the patient tried out at regular work while under sanatorium regimen and medical supervision. This idea will be brought up in the "economic" portion of this paper. From the medical point of view, our conclusion is that we cannot consider the history a factor in diagnosis as we were accustomed to do.

The post-sanatorium history in these patients who come back for observation or treatment, shows, as would be expected, that the prognosis is best, that is, the incidence of relapse is lowest, in the minimal group; not so good, but quite fair, in the moderately advanced; and poor in the far advanced. The results of former experience are confirmed, that the far advanced tuberculosis patient must, in a great majority of cases, be prepared to face a lifetime of semi-invalidism, being cared for and spared the ordinary exertions of trying to "make a living" for an indefinite period of time. The moderately advanced, if he can persist in treatment long enough, resume his exertions only gradually, and continue to regulate his life carefully, having periodic medical examinations, stands about a fifty per cent chance of avoiding relapse. The minimal, if his trouble becomes well arrested, may usually resume a normal life with safety.

It is readily observed, in ex-service patients, that many of them do not get the most out of their period of sanatorium treatment, do not take their case so seriously as the civilian, until they have had a serious relapse, or are away down, physically, and in almost hopeless condition. The civilian, who feels that he can afford to stay but a limited time, and must recover his health and support himself and his dependents, gets better results, generally speaking, from a given period of treatment, than the ex-service patient. There are, of course, exceptions to this comparison. And we find among our readmissions some men who during their first treatment were restless, and negligent of "the cure" and impatient with its necessarily strict regimen, but who have learned since discharge the seriousness of facing life with a disease-handicap, and the easiness with which one may bring about relapse. These men return with a new viewpoint, and a determination to settle down and take the treatment faithfully. It is well that, in a few cases, it is not yet too late. In others, unfortunately, it is. Faithfulness in "taking the cure" being equal, the ex-service patient responds to treatment as well as the civilian, and stands fully as good a chance of recovery; that is, there is no clinical difference in the type of case, between that due to or aggravated by military service and that acquired in the ordinary civilian life.

Another conclusion we have made, and one which would seem obvious, is that the discharged patient benefits greatly by the system of regular medical examination at six-month intervals; also, that it is best to have these examinations made at the institution where he has received his former treatment, where the physicians know his case, have his records

and former X-ray and physical findings, with which to compare his present condition, and where every facility for examination is at their disposal.

In the 66 cases in which relapse occurred, the causes to which patients attributed their relapse are given in table 12.

Six per cent of our relapses followed surgical operation. Though the tendency of certain anesthetics to aggravate a tuberculous process in the lungs is well known, we think it worth while to reiterate the advice that in all such cases gas-oxygen shall be used when a local anesthetic is not advisable.

It will be noted that 27.3 per cent of relapses are directly attributed to intercurrent respiratory diseases, and this does not include those in

TABLE 12

Apparent causes of relapse

Unsuitable work or too long hours of work	18 or 27.3 per cent
"Colds," respiratory and other diseases	18 or 27.3 per cent
Insufficient pension	17 or 25.8 per cent
Pension reduced too sharply	5 or 7.6 per cent
Surgical operations	4 or 6.0 per cent
Did not know they had tuberculosis	2 or 3.0 per cent
Treatment incomplete	1 or 1.5 per cent
Delay in re-treatment	1 or 1.5 per cent
Mental condition	1 or 1.5 per cent
No known cause (natural course of the disease)	20 or 33.0 per cent

(Only the 66 *Relapse* cases are included in the above table, but several patients belong in both of two classes, giving, for instance, both "unsuitable work" and "loss of pension" or "colds" as the causes of their relapse).

which "colds" were indirectly causative. This emphasizes the need of warning our patients, even when treatment is completed, especially to avoid catching colds, as these infections lower resistance and may have a most unfavorable influence on the course of the tuberculous disease. Herein is the danger—one of the dangers—of advising these patients to "get work out of doors in the fresh air." And, in addition to the danger of exposure to cold and wet, the fact has to be considered that most out-of-door work is heavy and laborious, putting too great a strain upon a patient whose disease was at any time well advanced.

It seems inevitable that the other largest percentage of relapses should be attributed to "unsuitable work." Five of this group have no pension complaint, but overworked for other reasons than lack of pension.

Nearly all in this group, however, say that they "gave out" because their pension did not keep them and because suitable work could not be found at which they could make a living.

The economic problem, the question of support, is the outstanding consideration in a study of readmission and relapse. Because the government and people of the country are pledged to care for and, when possible, to reëstablish the disabled ex-service man, this type of case presents material for study which is not brought before us in the case of civilians. But the problems of the tuberculous are much the same for all, and the lessons learned in dealing with ex-service patients may be utilized for other needy citizens.

It is granted that the Canadian people have dealt generously with their war veterans in the matter of institutional care and pensions. That there is, in a few individual cases, ground for complaint that pension awards have been delayed or insufficient or too abruptly reduced, does not do away with the fact that the Board, which has to deal continually with many thousands of cases, puts its best judgment and efficiency into a careful study of each claim and attempts to do at least exact justice to all.

While the ex-service patient is in the institution, the expense of his treatment and care is met by the Department of Soldiers' Civil Reëstablishment, from which also he receives pay and allowance for his dependents. There is no time limit; the patient with advanced tuberculosis who is entirely disabled may remain at the institution indefinitely, so long as he is content to live its necessarily regulated life. When he desires to go home, he is given an adequate pension, and he may be readmitted whenever the Department's physician so advises, no matter how bad his condition.

In the more favorable cases the patient is kept at the institution until his disease is arrested and he may hope to go on to complete recovery or until he is physically fit to make an attempt at reëstablishment in life. If we had in connection with the sanatorium some means for getting him to make this attempt while he is there, he could be kept longer and put more firmly on his feet before he is sent out. As it is, many a patient who is in fairly good shape when discharged, fit, it may be, for three or four hours' work a day, who, with sufficient rest and good food, should go on to recovery, fails to do so. His pension for the first six months, often continued for a year or more, is supposed to tide

him over the part-time period, while he is gradually accustoming himself to regular work and normal living. This is a good theory, but it rarely works out. Employers do not want a part-time man, and there is no definite place for him among his fellows; he is neither worker nor patient. The ambitious type of man and the man who is responsible for a family's support, will not stand this, but takes such work as he can get, probably full-time work and often unsuitable; and sooner or later he is back at the sanatorium in worse condition than ever, with a long and perhaps hopeless illness before him. The other type, knowing that he should "take care of himself," idles around for months, in a purposeless way of living which has a most detrimental effect upon the spirit and morale of any man. Then, when the time comes for his pension to be reduced, he is forced to go at once to full-day work, in this flabby mental and physical condition, and soon back he comes to the sanatorium, either with a genuine breakdown or with the hope of pay and allowance or a raise of pension.

Who is certain that his own courage and initiative would be better under the same circumstances? Let him cast the first stone. The successful and the fit, those who are better equipped for living than they, owe these men, not criticism, not general advice founded upon good theories, but *suitable employment.*

It is true that an honest effort was made to provide vocational re-training for tuberculous war venterans. But, judging from our study of readmissions, it has not been a practical success. Whether because the courses chosen were not adapted to the patients' condition, or because, after the course was finished, work could not be obtained, or for other reasons, we find that, while 85, or 42.5 per cent, of our readmitted men took a course, only 15 (17.6 per cent of the 85) made any use of it after it was completed. Eleven of these worked at the occupation a short time after the course was finished, then gave it up; leaving four, or 2 per cent, of our readmitted men who permanently took up the new occupation. Fifteen, or 17.6 per cent, of those who took a course broke down in health during the re-training, and did not complete it. It may be said that a fair judgment of the success of re-training cannot be made from readmissions, as naturally it is the unsuccessful who come back to the institution. This is to some extent true; but it should be remembered that only 66 or 33 per cent of these readmissions represent men who relapsed; that a considerable proportion of them returned only for observation; and that 67 per cent of them were successful,

at least in the way of keeping up their health after discharge from the sanatorium (see table 7). Moreover, it is the unsuccessful that we specially wish to study, their needs that we are trying to understand and meet. Happily, it is true that the majority of our patients are reëstablished or cared for by their families or in some way absorbed into the civilian population, and the sanatorium sees them no more. For these we make no plea. It is not of these we are writing; and we do not know precisely how the reëstablishment, in each case, was brought about, though we are now getting some information along this line from the pensioners who are sent to us for examination. There are lessons to be learned from follow-up study of all discharged sanatorium patients and more of it should be undertaken by our institutions.

An exhaustive report of the schemes and suggestions for "after-care," that is, for aid in reëstablishment after sanatorium treatment, for the tuberculous ex-service patient, was prepared, in 1920, after careful study of the subject in England, Canada, and the United States, by the late Col. (Dr.) William M. Hart, for the Board of Sanatorium Consultants and by them presented to the Canadian Government Department of Soldiers' Civil Reëstablishment. In it he dealt especially with plans for providing "sheltered employment," workshops, farm and industrial colonies. As Dr. Hart well put it,

> The results of sanatorium treatment are frequently dissipated by conditions and environment after discharge. . . . . Sanatorium treatment alone cannot produce the best results. . . . . As a part of the after-care of discharged patients, suitable employment is most desirable on therapeutic, economic and moral grounds. Philanthropists will occasionally employ a few; for the majority "sheltered employment" should be created. It is an individual problem, and assistance to the individual in finding a suitable opening is sometimes all that is necessary. For city-dwellers the substandard workshop has advantages over some other schemes. But to take the patient from the open-air life of a sanatorium and place him in city conditions is not, usually, desirable. The substandard workshop should be introduced cautiously, at strategic points, on an experimental basis.

The Report includes descriptions of one or two of the very few shops of this nature operated on the American continent and in England. The *Altro*, a garment shop in New York City, which grew out of the investigations of a committee which disclosed the fact that 52 per cent of the results won at a certain sanatorium for the tuberculous were wasted

through the forcing back of its recovered patients into industrial conditions detrimental to their health, has actually become self-sustaining. But it cannot be expected that schemes for sheltered employment of the tuberculous will be paying enterprises, in a primarily financial sense. Another workshop for the tuberculous in New York is that of the Reco Manufacturing Company, which is subsidized by the National Tuberculosis Association and assisted by the Federal Board of Vocational Education. The trades selected as suitable for teaching and work here were watch-repairing, jewelry-designing and manufacturing, and cabinet-making. Patients at the Reco shop have done well in maintaining health and learning trades, but the shop shows a deficit from the standpoint of self-support. In England the Wimbledon shops (especially for tuberculous soldiers and sailors) provide in one part training and in another permanent employment, under "sheltered" conditions. The occupations include carpentry, cabinet-making and basket-making. The Government is to supply the deficit in running expenses.

"Such a shop, to be successful, would have to be situated where raw materials, transportation and markets are available, and where there is a sufficient number of patients to warrant it." The only substandard workshop for tuberculous ex-service men in Canada, so far as we know, is the Vetcraft Shop at Hamilton, which, we hear, has been successful from the point of view of patients' health and reëstablishment, and which is making a reputation for its products.

As to Farm Colonies, there are several in successful operation, one at Hairmyres, near Glasgow, Scotland, consisting of 300 acres of arable land and 6000 acres of forest, where 250 to 300 patients concentrate upon stock-raising and forestry in addition to ordinary farming. There is another in connection with the Royal Victoria Hospital of Edinburgh. A farm colony is conducted by the Y.M.C.A. at Kinson in Dorset, England, for 21 ex-service patients. And at Eudowood Sanatorium, near Baltimore, U. S. A., there is a most successful attempt to carry on a modified form of Farm Colony, largely for therapeutic purposes. But Dr. Jane Walker expresses the consensus of expert opinion when she states that a "Farm Colony for Consumptives" is impracticable because "farm work is an arduous skilled occupation and as such can be undertaken by few tuberculous people, during their treatment or after." This was the conclusion reached, also, by the Sanatorium Consultants, who looked pretty carefully into the possibilities of fruit-farming or orcharding, even in the most

favorable regions of British Columbia and the Annapolis and Cornwallis Valleys of Nova Scotia. Even less desirable is general farming in the middle West of Canada.

The Industrial Colony combines the training and employment of the substandard shop with provision of suitable living and housing conditions, preferably in rural surroundings. Its object is to prolong the treatment of the sanatorium while training and hardening the patient to work up to his capacity and with minimum risk to his health. The Mill House at Maryland, England, in connection with the East Anglian Sanatorium, provides a factory where toy-making, chair-making, light metal work and the designing and making of art jewelery are carried on. Dr. Walker hopes here to see a model village community where patients and their families may settle permanently. This is an excellent illustration of the Industrial Colony idea. And its possibilities of success, especially in Canada, greatly exceed those of the Farm Colony. There is, however, a still better idea in a Combined Industrial and Farm Colony, in which such occupations as poultry-raising, bee-keeping or allied activities might be developed to supplement the industrial employments. Perhaps the most widely known and successful example of this combined type is the Colony on the Papworth Estate, England. Here the Hospital, the Sanatorium, the Training Colony and the Permanent Settlement are parts of one excellent system for the care and rehabilitation of the tuberculous. Some consider this the ideal way for caring for the tuberculous—in a community gathered around the sanatorium and in close coöperation with it—the sanatorium being a link in a chain by which the patient passes to such degree of self-support as he is capable of at his best. No matter what form after-care or sheltered employment may take, an essential is expert medical supervision, and this can nowhere be so well carried out as in a community connected with the sanatorium. In Canada such a scheme was enthusiastically supported by a certain number of patients—most of them married men—at the leading sanatoria for ex-service patients. But, because of the great initial cost and the comparatively small number of patients willing to enter it, this colony did not materialize. However, while relapses still go on, and are likely to go on, and while so large a proportion of our discharged patients fail to find work suitable to their capacity, it would seem that some attempt to provide practical instruction and part-time working facilities in connection with the sanatorium might be tried out at less expense than the elaborate schemes formerly planned.

The problem differs in different parts of Canada and each Province will no doubt have to work out a system for itself, but in Nova Scotia, at any rate, we believe that a beginning should be made by the acquisition of a small farm in connection with the Sanatorium at Kentville and the establishment of a workshop on the Sanatorium grounds, with competent instructors in charge of both; and through the creation of an Employment Bureau or Committee consisting of men and women fully in touch with industrial conditions, acting always in consultation with the physician who has had the patient in charge.

It has been maintained that a tuberculosis sanatorium should have its own farm and raise its own food. Where this is possible, the same farm could be used for the instruction of patients. But, where the larger farm cannot be undertaken, adequate training in such occupations as bee-keeping, poultry-raising, vegetable-gardening and the growing of small fruits and of seeds as well as in the proper marketing of these products, could well be given on a farm of about ten to fifteen acres. From consultation with the superintendent of the Dominion Government's Experimental Farm near Kentville I learn that such a farm, with the modest equipment necessary, would involve an initial outlay of about fifteen thousand dollars. Mr. Blair, who courteously gave much attention to our questions and whose judgment in such matters is of the greatest value, speaking of our patients, says, "It would be well to direct their training to intensive work on a small area and to the employment of the best-known methods. The farm might consist of half an acre for small or bush fruits, 3 acres for strawberries ($1\frac{1}{2}$ acres rotated with clover), 4 acres for vegetable gardening (2 acres rotated), half an acre for bee-keeping and 2 acres for poultry. I do not see why such work cannot be taken up profitably by your part-time workers."

Unfortunately, in our climate, the season of farm-and-garden work is only about half the year, but the workshop would be available the year around. In it a very few occupations would be taught, chosen for their suitability for the patients and the demands of the local market. In the winter, too, could be given talks on the work done on the farm and class instruction which would be helpful to the patients as wage-earners. It may be that the partly disabled, instead of becoming discouraged by their physical disability, could be led to balance it by extra knowledge and skill.

It is to be hoped that many of the occupations taught could be carried on at the patient's home and with the assistance of his family.

A large proportion of patients in a rural population such as ours have or can secure a few acres of land. Some of the workshop handicrafts could profitably be taken up in the home aided by other members of the household, to the benefit of the family purse.

In the case of civilians, the Employment Committee would have to act in collaboration with the County Clinic, under the medical supervision of which the patient would remain after his discharge from the sanatorium,—indeed, whether he ever enters an institution or not.

We know well that, while many reports are prepared—and many, even, are read, and a few, like that of Dr. Hart on *After Care* are mines of information and suggestion,—resultant action is quite "another story." Nevertheless, urged by our intimate knowledge of these cases, and not without faith in the practical interest of their countrymen, we hark back to the needs of our patients as revealed in their readmission histories.

We are convinced that it would pay the country financially, in the long run, to undertake the moderate expenditure necessary to train and find work for these men, thus preventing the long periods of expensive treatment which too often follow relapse, and enabling them to "produce" to their best capacity. It is surely "bad business" to allow so great a percentage of the money and effort spent in sanatorium treatment to be wasted after discharge. As we have said, the totally disabled are provided for. But the partly disabled, including the patient with "open" and technically incurable but quiescent disease, who is able and usually anxious to do some definite, interesting work, and the curable patient who must go through a period of regular part-time work and gradual increase of exertion if he is to win back safely to normal living,—the problem of employment for these men cries for solution. We should include in this class those of the nontuberculous among our readmission cases whose respiratory disease, usually bronchitis, constitutes at times so great a disability that they cannot make a living in the open labor market, and yet who are not subjects for continued sanatorium treatment.

The more we know of these patients, their lives and prospects, the more poignant seems their handicap. In so far as they are untrained, dependent, unfit, or lacking in whatever makes a complete man's equipment, we must consider them as children, wards of the nation. The parent, attempting to equip his children for living, does not simply give them a money allowance and turn them loose; neither does he keep them in idle-

ness in his own house forever. The development of spirit and character is at least as important, both to the individual and to the state, as the mere sustenance of the body. And so, even if the nation could afford to give one hundred per cent pension to all of these men for life, or to keep them in sanatoria as long as they live, we should not be doing our full duty to them—and to their children, for many of these men do not hesitate to marry and assume the responsibility of a family. What is needed is suitable employment. There is nothing under heaven like the interest and inspiration of work well done; nothing to cure the war neurosis and to increase a man's self-respect and morale, his sense of responsibility, like the feeling of being something and doing something worth while toward his own support and that of his dependents. Some of them may have to be educated up to it; some will need teaching and training; many will not. Many are already doing the very best they can.

We are not suggesting that employers shall take these part-time workers into their offices and factories, though, when the Employment Bureau gets to work, it may find a few employers willing to do even this; a few who do not forget the promises made in recruiting days, when the boys were told that jobs would be waiting for them when they came back from the war. The number of these patients is not so great that finding work for them will demoralize the labor market or have any appreciable effect upon the "unemployment problem."

And just here it may be said that, if conditions in the labor world were better, many more of our ex-sanatorium patients would be able to take up full-time regular work. But where there are ill-ventilated working places, dust-hazards, long hours and the necessity for keeping up a forced "pace," even those with arrested disease must often be forced back into invalidism. For these, as well as for the definitely under par, "sheltered" employment and part-time work will have to be provided.

As we have said, the foundation should be laid while the patient is at the sanatorium. There, at the proper stage in his recovery, work should be prescribed as part of his treatment, not to be shirked. While the primary object of this work-treatment would be therapeutic, providing a gradual rise from the mental and physical flabbiness of the rest-cure period and a development of the capacity and habit of work, under medical supervision, at the same time the man would be taught something which would increase his value as a worker and help to put him in the way of permanent occupation after discharge. Each patient's case, his plans and possibilities, would be studied, with the advisory aid of the Employment

Bureau aforesaid. Wherever possible, his new work should be along the lines of his former occupation or one allied with it. He would begin with, say, two hours' work a day, increasing gradually, provided his condition warranted it, until he had reached his best capacity; meanwhile receiving his regular examinations and continuing to live according to the regimen of the sanatorium. This system would provide a sort of laboratory for the physician to try out the working capacity of the patient, and is, indeed, the only way in which the physician may be enabled to prescribe and advise accurately regarding occupations. There is no doubt that the average patient would develop a keen interest in any work supervised in such a way that he found himself becoming a better workman; especially so if he knew that he was practically certain of employment after his discharge.

That such an experiment can be tried out at an institution so favorably situated as the Nova Scotia Sanatorium, it is not unreasonably optimistic to hope. And, if results seem to justify it, a similar system could be introduced at other places. In our Province, because civilian and ex-service patients are treated together, it is possible that the cost of such an experiment would be shared by Provincial and Federal Governments.

The organized war veterans, the Red Cross, the Canadian Tuberculosis Association, any body of people interested in the tuberculous, would do well to think over and try to get some action upon this idea, which we believe to be full of possibilities for the welfare of our partly disabled citizens,—their all-around welfare, "mind, body and estate."

THE REHABILITATION OF ARRESTED TUBERCULOSIS CASES AT EUDOWOOD SANATORIUM[1]

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Just what measures to adopt to prevent relapse of arrested tuberculosis cases is a problem that has always given grave thought to all workers in tuberculosis. A large number of cases that have been treated at home, at our sanatorium as well as at other institutions, are constantly seeking readmission due to relapse.

The problem of rehabilitation of the tuberculous is not a new one; nevertheless it demands urgent attention before very great further strides can be made in our antituberculosis campaigns. Many patients could be prevented from becoming chronic invalids, and many lives could be saved, had the proper measures been taken to prevent their relapse. A great number could be made self-supporting and an asset, rather than a liability, to the community. At present we have patients who after their relapse go from one sanatorium to another, to spend their few months of miserable existence until death finally relieves them of their plight.

Among the factors involved in patients' breakdowns is, first, disregard of medical advice. There are patients who, after a short stay at the sanatorium leave against the advice of the physician as soon as the acute symptoms have subsided, and they have gained a few pounds in weight and feel fairly well again. These patients become very restless and go back to their homes, and in a number of cases go right back to work. The percentage of relapses in this class is very great because the disease has not been arrested and improvement is only temporary.

These patients soon break down and seek readmission to the sanatorium with their condition far worse at the second admission than when they first sought treatment. The remedy in these cases is this: The physician who treats a tuberculosis case either at home or sends it to a sanatorium should always have a talk with his patient and explain to him just

[1] From Eudowood Sanatorium, Towson, Maryland.

what the disease is, the necessity of taking the cure just as long as is necessary to acquire the desired result, and that an improvement in his symptoms does not mean that the disease is arrested. The physician must explain to the patient the importance of coöperation on his part and how he must be guided by the physician's advice at all times if satisfactory results are to be expected.

If the physician decides to send the case to a sanatorium he ought never to tell the patient the exact length of time he will have to spend at the sanatorium, because in a great majority of cases the course of the disease does not run as smoothly as was originally expected, and, as a result, the patient gets discouraged and leaves the institution whether he is fit or not. The length of stay should be judged by the physicians in charge of the case after they have had the opportunity to study the case. Many a patient has left the sanatorium when the disease was still active just because his home physician had told him that he would have to stay just so long. A great deal of good can be accomplished and many a patient saved from a relapse by a talk with him at the beginning of the disease, because at that time he is apt to be most impressionable.

In the second place, there are those cases that have been treated at the sanatorium until they have been pronounced apparently arrested and have been discharged without being put through a course of graduated exercises and work under medical supervision to test their endurance. It is in this category that the average sanatorium case falls.

The situation, as I see it now, is this: The patient, having undergone treatment for a variable time and fortunate enough to have had his disease arrested, is discharged from the sanatorium with the usual advice to look for a light outdoor job. How absurd is this advice to the average individual in moderate circumstances! How many people are there who can find that ideal light outdoor job? Very few, it must be admitted; and what happens in the majority of cases is that the ex-patient, after trying to get this ideal job, fails, and is obliged to return to his old trade to earn his living with the inevitable result,—a relapse. In the case of the few fortunate ones that are independent the problem is easily solved and, as a result, the chances for a relapse are very much diminished.

It is not using good judgment to allow a person to go back to his regular work as soon as he is pronounced an arrested case, because, although he may be free from any symptoms of activity while living under ideal conditions at the sanatorium and not doing any work,

it may be different when he goes home. There he has to shoulder the responsibility of the household, and in going back to work at his old job he must compete with his fellow-workmen on even terms, and with a physical handicap that will not permit the latter. In most cases the result is that he breaks down in a few months. Not before the patient gets toughened again and put into shape by a course of graduated exercises, and made to do some work so many hours a day so that the effect of labor upon his condition can be watched, is he fit to be discharged and allowed to take up his work again.

After all, the test of condition on discharge is not so much the findings of auscultation, pulse and temperature, as the amount of work the patient can do without fatigue. The acid test is going to be how long will the ex-patient be able to keep up at his work and support his family without a relapse in his condition.

It is a much better plan to keep arrested cases a few months longer under observation and put them through a course of graduated work, so as to give them a chance to build themselves up again and to make them feel confident that they can still do a day's work without feeling exhausted.

Relapse in tuberculosis is in proportion to the stage of the disease; in other words, the earlier the lesion the less the chances for a relapse. That all arrested cases may do some graduated work under medical supervision, every sanatorium ought to have some kind of workshop or work-colony to serve the purpose of rehabilitation. There the patient should be toughened and prepared to resume his former occupation, if it be suitable, or taught a different trade that will be consistent with his physical condition. Not until the sanatorium does rehabilitate its patients will it perform its full duty toward the public.

Whether or not the ex-patient should return to his former occupation will depend upon the work he did before entering the sanatorium. In all cases it is advisable for the patient to resume his former work if possible, because he is adapted to it and can go right back to it and earn a living. In many cases, however, it is not advisable for the patient to resume his former occupation and then he ought to be taught a new trade.

The following trades are suitable for arrested tuberculosis cases: barber, bookkeeper, decorator, jeweler, clerk, chemist, telegraph-operator, cap-maker, etc. I do not see any objection to a person going back to

any of the above trades, but if the patient was employed in a shop at very heavy physical labor, such as boiler-making, blacksmithing, steel-working, etc., then he should change trades.

What rehabilitation will do for even advanced cases can be judged from the fact that we have working for our sanatorium about 50 ex-patients and many of them have been with us for the last ten years, most of them doing work an able-bodied man would have to do. I have no doubt that had some of these patients left the sanatorium as soon as they were pronounced arrested cases they would not be alive to-day. Most of them do a full day's work and are in splendid physical condition. Among these ex-patients we have carpenters, cleaners, chauffeurs, engineers, firemen, housekeepers, maids, nurses, orderlies, painters, poultrymen, seamstresses and watchmen. A number of them could leave the institution now and earn a living in the city if they should so desire, but, realizing the advantage of living in the country and being under medical supervision all the time, they prefer staying here.

A training school for nurses has been established at Eudowood Sanatorium for the young women who have had the disease arrested. The school was founded in 1908 and since then 35 nurses have been graduated. Thirty-two of them are alive and well to-day, and many of them are occupying some very important positions in some of the leading sanatoria in the country. Three nurses have died, one during the influenza epidemic and the other two of tuberculosis after nursing the tuberculous for about seven years. One of the head-nurses at Eudowood is our own graduate, who, after having been a patient for about twenty-five months, was given up as a hopeless case, finally recovered and took up nursing, and has been in charge for the last five years.

In the last few years many workshops for the rehabilitation of arrested tuberculosis cases have been established and have met with great success. Landis (1) says

> In an effort to acquire further experience with the practical problem of employing arrested cases of tuberculosis we organized and operated for about two years a small shop for the manufacture of ready-made wearing apparel. The operation was conducted in two periods. The first period was a failure in the financial sense. In the second period enough was done to show that better financial results might be secured under favorable conditions. From the medical point of view our experiment was an unqualified success.

A workshop for the rehabilitation of tuberculous ex-service men was opened in Long Island City by the National Tuberculosis Association, the New York Tuberculosis Association and the Federal Board of Vocational Training. Such trades as watch-repairing, jewelery manufacturing and skilled cabinet-making are taught. Of the results obtained at this shop Thorburn and Billings (2) say, "Industrally our results are very satisfactory; in each of the departments there are men doing excellent work; in all departments there are some men who are having the finishing touches put upon their knowledge of their craft; there are several in each group, who, if it were necessary, could now earn their living from their trade."

In establishing the farm-colony at Eudowood Sanatorium Jacobs (3) said, "The main purpose has been to introduce some form of after care in the nature of healthful occupation, where the patients might feel themselves again self-supporting and allow them time for making permanent the result for which they and the sanatorium have been striving." This farm-colony was begun by Forster in 1908 and has progressed steadily ever since. About 250 ex-patients have been rehabilitated and returned to their homes again fit to take their place in society and earn a living, with the danger of a relapse greatly diminished. When the farm-colony was first established the following specialties were taught: dairying, horticulture, packing and canning, trucking, and swine and poultry culture. In the last five years, however, the colony has specialized in poultry-raising, exclusively, because the patients like this kind of work best, and it is cleanest and not too laborious. It has also proved to be a paying proposition. The great strides that have been made in the last few years in the farm-colony at Eudowood Sanatorium can be judged by comparing the situation then and now.

The living quarters originally consisted of an old dilapidated farmhouse that required repairing all the time. In the basement were three rooms which were converted into an incubator-room, supply-room and storage-room for the packed eggs, respectively. The poultry department consisted of a mongrel flock of 75 fowls, one regular hen-house, two converted wagon-sheds, three brooder-houses and a granary. The farm-colony now consists of a new $25,000 home, containing the latest modern improvements, such as sun-parlors, showers, bathrooms, sleeping-porches, dressing-rooms, etc. The poultry department now consists of a flock of 15,000 Danish White Leghorns, an 18,000 egg

incubator, 5 large modern hen-houses, 10 brooder-houses and a large new granary.

That the poultry farm has been a financial succes may be judged from the following table:

YEAR	NUMBER OF EGGS	POUNDS OF CHICKEN	POUNDS OF DUCK	POUNDS OF GEESE	PROFIT
	dozens				
1918	8,293	2,897	330	223	$512
1919	8,866	2,333	281	309	545
1920	11,029	5,105	203	411	1,092
1921	11,285	4,933	272	662	1,100
1922	12,158	4,890	332	445	1,200

The farm-colony at Eudowood Sanatorium has proved to be a medical, social and financial success. First, by rehabilitating arrested tuberculosis patients it has given them a new lease on life; secondly, it has shown that even advanced cases with graduated exercise can do a certain amount of work without detriment to their condition. Indeed, a certain amount of work is even beneficial to them. And, thirdly, the sanatorium has always been supplied with new-laid eggs and fresh-killed chickens, geese and ducks at a lower price than the market cost, and by its profits it has helped to maintain the patients. It is to be hoped that the time is not far off when every sanatorium will have some department of reconstruction where its arrested cases will be rehabilitated so that they will again be able to take their place in society without fear of a relapse.

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(2) THORBURN AND BILLINGS: Tr. Nat. Tuberc. Assoc., 1921, 177.
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A CHEMICAL BASIS FOR THE TREATMENT OF TUBERCULOSIS

EXPERIMENTS ON THE ACTION OF STEAPSIN AND INSULIN ON TUBERCLE BACILLI[1,2]

LOUISE G. ROBINOVITCH AND GEORGE W. STILES, JR.

The chemical composition of the tubercle bacillus has been studied more carefully and extensively than that of most pathogenic bacteria. All investigators agree as to the unusual resistance of this bacillus to therapeutic and chemical attack. DeSchweinitz and Dorset (1) found it to have waxy and fatty constituents and many workers have confirmed these findings. Goris (2) made a more detailed chemical study than did his predecessors. The main and dominating fact is the existence of a protective waxy part, either as coating or as a part of the whole structure of the bacillus. Wells, DeWitt and Long (3) published a review of the literature of the chemistry of the tubercle bacillus and tuberculosis up to 1923. The net result of their review of the structure of the bacillus may be summarized as follows: that it is characterized by a high lipin content; that "the lipin is, apparently, not true fat for the most part, but an ester, or mixture of esters, of the group of waxes;" and that it is difficult to saponify this wax. According to Buerger (4), the protective endowment of this bacillus results in the following situation: "Whether applied as a coating to the surface of the bacillus, or diffused uniformly through the protoplasmic mass, it must render the germ less permeable to destructive agencies and therefore more resistant to intracorporeal lysis."

Wells, De Witt and Long also state "the presence of free fatty acids has several times been emphasized" (5), and that "The bulk of the lipin is thus of the nature of wax, consisting of esters, of alcohols of high molecular weight, chiefly one of the composition of $C_{29}H_{55}OH$, with various fatty acids, apparently largely lauric and palmitic acids" (6). In view of such a protective substance they summarize the matter of

[1] From the Chemical Laboratories of the Colorado School of Mines, Golden, Colorado.

[2] By invitation, the chemical part of this paper was presented before the Denver Section of the American Chemical Society, by Doctor Robinovitch, January 30, 1924.

treatment as follows: "We have included in the section whatever work we have found in the literature in which biological experimentation with certain chemical substances has been used in an effort to find a chemical cure for tuberculosis. . . . . As has been already shown—*no specific chemotherapeutic agent has been found for tuberculosis. No chemical yet used has cured the disease in the experimental animals employed*" (7) (*italics the author's*).

In November, 1921, two years before this statement appeared in print, I[3] began animal experimentation for the purpose of determining a chemical basis for curing tuberculosis. The president of the Colorado School of Mines, Dr. Victor C. Alderson, extended to me the facilities of the school for this research. Throughout my investigations the professors of chemistry and physics at this school have continued helpful. By accident, I met the bacteriologist of the U. S. Bureau of Animal Industry, Denver, Colorado, Dr. George W. Stiles, who volunteered to do the bacteriological work for me and has graciously continued this since then. I feel greatly indebted to him for his aid.

The course of the work was as follows: I bought the animals required in the experiments; Dr. Stiles infected them at the U. S. Bureau; I carried the animals to Golden, where I housed and treated them; in due time I carried the animals back to Denver, to the U. S. Bureau, where Dr. Stiles autopsied them.

My first attempt to destroy the tubercle bacillus in the living body was by means of radioactive salts, quantities of which I acquired from time to time. Looking solely to the lethal qualities of the radioactive effects, I reasoned that the alpha particles, carrying enormous potential powers for ionization (8) (9) (10), should be available as agents to ionize and destroy the part of the tubercle bacillus that has withstood chemical attack. I deemed it useful to exhaust this theory. Guinea pigs were infected with tuberculous material; intraäbdominal inoculations were made or the the lungs were infected by way of the nasal passages (11). Treatment with radiaoactive salts was administered both by mouth and hypodermically, at proper intervals, to allow elimination of the radioactive salts. The salt chosen was thorium nitrate. It was tested electroscopically by the alpha-ray effect and was compared to that of standard carnotite ore, and this effect of the salt was found to be

[3] Since the experiments on chemistry and treatment related in this paper were developed by Dr. Robinovitch, the first person singular is used in discussing these topics.

equivalent to 14.5 mgm. radium per ton. This is equivalent to 1.6×10^{-6} millicurie per 100 mgm. thorium nitrate. Prof. L. D. Roberts's assistant, Mr. Samuel Eldridge, made this test.

Thorium nitrate is soluble in water. When diluted with water the radioactive emanation is freely liberated; the alpha and beta particles and the gamma rays have their fullest effect on substances subjected to their action in the solution.

Accordingly, the tubercle bacilli, in proper concentration, were put into this solution of thorium nitrate. The strongest concentration used was that of one to fifty of sterile water. This concentration of the radioactive salt was not used at random. Many series of chemical tests, covering a long period, during which various pathogenic bacteria were subjected to the action of this radioactive salt, had taught me that a concentration of one to fifty was necessary to produce an effect on germs in an organic medium, such as blood, milk or bouillon.

The tubercle bacilli were put into this concentrated solution of radioactive salt, and the mixture was well agitated by hand in a container for a period of from a few minutes to two hours. I expected that during such a length of time the radioactive element would have sufficiently come in contact with the tubercle bacilli to destroy them. This mixture of bacilli with radioactive salt was then injected into guinea pigs, abdominally or into the nostrils. Other guinea pigs were injected with the same mixture after it had been kept in the container three and one-half days or, more precisely, eighty-four hours. The aim was to ionize or destroy the tubercle bacillus as completely as possible by the fullest effect of the alpha particles' activity.

We know that an emanation from radioactive salts has catalytic properties, both as regards organic and inorganic matter. Following the generally accepted view of the effects of the impact of radioactive particles on microörganisms, it was natural to expect that direct contact of the emanation with the tubercle bacillus would cause a piercing of the protective coating and destruction of its life.

Other guinea pigs were injected with "straight" tuberculous emulsion or suspension. These animals were not treated in any way. They were the controls. Still another series of guinea pigs was injected with tubercle bacilli; but these animals were treated with radioactive salts, both by mouth and hypodermically. At first the dose administered was small, but it was soon increased to 50, 100 and even 200 mgm. These were given at proper intervals, to allow elimination of the salt from the ani-

mal's system. The larger doses were soon found to be excessive: when 200 mgm. were injected in solution hypodermically, the salt produced a peculiar burn of both the skin and underlying tissues; in the normal animals they assumed a pearly white color; when touched, the dry mass disintegrated. In the majority of the infected animals ulceration followed. The smaller doses, about 50 to 80 mgm. were then used.

These experiments consumed the first winter and spring. The net result was as follows:

1. The control animals that were not infected with tuberculosis, but were given the same doses of the thorium nitrate as were the infected animals, were in excellent physical condition.

2. The control animals that had been infected with tuberculosis, but were not treated at all, died of generalized tuberculosis.

3. The test animals that had been infected with tuberculous material which had been treated previous to the injection with the radioactive salt, died of tuberculosis, with marked destruction of the viscera. So marked were these tuberculous lesions that Dr. Stiles, and others of the U. S. Bureau, who are accustomed to seeing tuberculous infection in animals, said that they had never observed such destructive processes caused by tuberculosis in guinea pigs.

4. The guinea pigs injected with "straight" tuberculous material, and treated with the radioactive salt, as explained, showed severe tuberculous destruction of their viscera similar to that found in the animals injected with tubercle bacilli treated with the radioactive salt previous to injection into the animals.

In seeking for an explanation of the above results which seemed to belie my theory, it occurred to me that the radioactive salt was acid and that the severer tuberculous lesions in the animals treated with the radioactive salt were caused by the acid nature of the medicament,—the very agent that otherwise should have destroyed or hydrolyzed the tubercle bacillus and accomplished a cure; and that in the treatment of bacilli with a waxy covering a neutral or an alkaline material was necessary.

I then asked Prof. Wilfred W. Scott to prepare for me a neutral or alkaline salt of thorium, soluble in water. I thought that a thorium iodide might answer my purpose, both on account of the radioactive thorium and the iodine. The method used was that of converting thorium nitrate into thorium hydroxide by means of ammonium hydroxide; the obtained thorium hydroxide was washed with water until no trace

of ammonia remained; then the filtrate containing the thorium hydroxide was treated with the theoretical amount of hydrogen iodide required according to the reaction:

$$Th(OH)_4 + 4HI = ThI_4 + 4H_2O$$

The thorium iodide so obtained gave an acid reaction, so that a large excess of thorium hydroxide was necessary to suppress ionization sufficiently to give a neutral reaction. This neutrality, however, did not last long, as the solution on standing became acid; we again faced the acidity that was so favorable to the growth of the tubercle bacillus; besides, both the short-lived neutral or alkaline preparation and the acid one were fatal to the animals injected with these chemicals. (We have in mind the preparation of thorium carbonate or borate. The subject seems to be of interest to the student of radioactive chemicals and we hope to treat of it at some future time.)

As to the use of solutions of radioactive salts to harness the ionizing power of the alpha particles, the following situation presented itself: Besides the complexity of the chemical reactions involved in the solution by reason of ionization, the alpha particle itself carries a double charge of positive electricity. We know that the positively charged electric conductor gives an acid reaction. As the electric charges of the same denomination from all sources are alike, it appears that the alpha particle is a constant source of acid reaction. Figuring chemical reactions in terms of electric charges, we recall what Stieglitz (12) states on the subject: "All of the oxidation and reduction reactions which have been discussed may, in fact, be effected by the use of an *electric current* in the place of chemical agents: ferrous salts, for instance, are *oxidized*, at the positive pole, by the current, to ferric salts. . . . . Ferric salts are *reduced*, at the negative pole, to ferrous salts."

So the work up to this time demonstrated that in tuberculosis it is dangerous to use acid treatment, whether as a common acid, as a positively charged particle, or as any other positively charged chemical or element that gives an acid reaction (13). Such acid agents do not dissolve or saponify the waxy or protective matter of the tubercle bacillus, or of any other pathogenic microörganism of a similar nature. Not only is such acid treatment useless, but it is dangerous; many devoted investigators in this field heretofore have failed because this fact had not been settled. I think I am justified in declaring as an indubitable truth that *an acid medium favors the development of the tubercle bacillus.*

I pause to recall what has been said about the structure of the tubercle bacillus: "From all that may be gathered from the literature, true, neutral fats make up no great part of the bacillus . . . . on the other hand the presence of free fatty acids has several times been emphasized."

According to Aronson, Kresling and Goris, "the fat of the tubercle bacillus is already rancid fat, containing about 15 per cent of its weight as free fatty acids" (14).

Henning (15) concludes his researches on the condition of the blood in tuberculous patients as follows: "The 'residual' fatty acid of the blood was high; and since there was no lipemia, the presence of other forms of fatty-acid combinations than those ordinarily present is suggested."

If these fatty acids, together with the waxy structure, act as protectors of the tubercle bacillus against attack by medication, it is clear that *acid medication is contraindicated in tuberculosis.*

I may state, as an aside, that certain acid treatment was quite effective in attacking and killing a series of microörganisms that cause various other diseases. These tests were made in vitro only. The typhoid bacillus was destroyed in from one to two minutes; the radioactive salt may, therefore, under certain conditions, be a curative agent in that disease; other pathogenic bacteria that were killed in the test tube were cultures of diplococci, streptococci, colon bacilli, and a micrococcus from an influenza case. Possibly the cholera vibrio is readily destroyed by the same radioactive salts. This work will be published later (16).

Chemical consideration of diseases seems, then, to group the affections due to microörganisms into two distinct classes: (1) diseases amenable to acid treatment and (2) diseases not amenable to acid treatment.

The following cases of guinea pigs treated with radioactive salts illustrate the statements regarding the danger of acid treatment in tuberculosis:

1. GUINEA PIGS NOT INFECTED WITH TUBERCULOSIS, BUT TREATED WITH THORIUM NITRATE IN SOLUTION IN DISTILLED WATER

G. P. no. 3: Dec. 3, 1921, 1 mgm.; Dec. 10, 1 mgm.; Jan. 1, 1922, 10 mgm.; Jan. 8, 100 mgm.; Jan. 13, 80 mgm.; Jan. 19, 100 mgm.; Jan. 31, 100 mgm.; Feb. 7, 100 mgm.; Feb. 10, 100 mgm.; March 3, 50 mgm.; March 8, 60 mgm.; March 21, 30 mgm. Except on January 19, when the thorium nitrate was given hypodermically, administration was always by mouth. Animal in good condition; Dec. 3, 1921, weighed 542 grams; March 21, 1922, weighed 920 grams. Radioactive salt discontinued.

G. P. no. 4: Dec. 10, 1921, 2 mgm.; Jan. 1, 1922, 50 mgm.; Jan. 8, 80 mgm.; Jan. 13, 80 mgm.; Jan. 19, 100 mgm.; Jan. 27, 100 mgm.; Jan. 31, 100 mgm.; Feb. 7, 100 mgm.; Feb. 10, 100 mgm.; March 3, 50 mgm.; March 8, 60 mgm.; March 21, 30 mgm.; always by mouth. Animal is in good condition; weight Dec. 3, 1921, was 572 grams; weight March 21, 1922, was 945 grams.

G. P. no. 5: Dec. 14, 1921, 10 mgm.; Jan. 1, 1922, 20 mgm.; Jan. 8, 80 mgm.; Jan. 10, 80 mgm.; Jan. 13, 80 mgm.; Jan. 19, 100 mgm.; Jan. 27, 100 mgm.; Jan. 31, 100 mgm.; Feb. 7, 100 mgm.; Feb. 10, 100 mgm.; March 3, 50 mgm.; March 8, 60 mgm.; always by mouth except on January 19, when hypodermically. Animal is in good condition; weight Dec. 14, 584 grams; weight March 8, 1922, 845 grams. Temperature 98.2°. Treatment discontinued.

2. GUINEA PIGS INFECTED WITH TUBERCULOSIS AND TREATED WITH THORIUM NITRATE

G. P. no. 1: Dec. 3, 1921. Control to G. P. no. 2. Emulsion from tuberculous lymph node of cow. Injected intraäbdominally 1 cc. of dilute emulsion, same as in the test case, G. P. no. 2. Died Dec. 28, 1921. The autopsy showed marked tuberculous lesions of the liver and spleen.

G P. no. 2: Dec. 3, 1921. Injected intraäbdominally 1 cc. dilute emulsion from tuberculous lymph node of cow; same material as that used for G. P. no. 1. Twenty-four days after infection given by mouth 10 mgm. thorium nitrate in distilled water. Dec. 29, 1921, intraäbdominally, 10 mgm., and by mouth 10 mgm. thorium nitrate. Jan. 1; 1922, 10 mgm.; Jan. 2, 50 mgm.; Jan 8, 80 mgm.; Jan. 10, 80 mgm.; Jan. 19, 100 mgm.; Jan. 27, 100 mgm.; Jan. 29, 100 mgm.; Jan. 30, 100 mgm.; Feb. 5, 100 mgm.; Feb. 10, 60 mgm.; all by mouth except on January 19, when hypodermically. Died February 16, 1922. To date of death animal received 810 mgm. thorium nitrate.

Autopsy: Marked abdominal effusion; liver degenerated with tuberculosis. Seat of hypodermic injection of thorium nitrate, 100 mgm., shows destruction of the tissues extending to the muscle. Smear of pancreas shows acid-fast rods. Macroscopically the lungs, spleen and liver show tuberculous lesions.

G. P. no. 9: Dec. 28, 1921. Control to G. P. no. 11. Injected intraäbdominally 1 cc. tuberculous emulsion from liver of G. P. no. 1. Died February 22, 1922, of generalized tuberculosis of all the viscera.

G. P. no. 11: Dec. 28, 1921, injected intraäbdominally 1 cc. tuberculous emulsion from liver of G. P. no. 1. Given by mouth solution thorium nitrate, 10 mgm. Jan. 1, 1922, 10 mgm.; Jan. 2, 50 mgm.; Jan. 8, 80 mgm.; Jan. 13, 80 mgm.; Jan. 19, 100 mgm.; Jan. 27, 100 mgm.; Jan. 29, 100 mgm.; Jan. 31, 100 mgm.; Feb. 22, 100 mgm.; all by mouth. Temperature remained 104°F. regardless of treatment. Animal died February 22, 1922. Autopsy showed generalized tuberculosis of viscera.

G. P. no. 16: Jan. 17, 1922. Control to G. P. nos. 17, 18, 19, 20, 21, 22, 23. All of these animals received intraäbdominally 0.5 cc. tuberculous emulsion from cow's udder. This control animal died March 4, 1922. The liver and spleen were destroyed by tuberculosis; hemorrhagic effusion in the abdominal cavity.

G. P. no. 17: Jan. 17, 1922. Infection intraäbdominally same as no. 16. Given hypodermically 200 mgm. thorium nitrate in 1 cc. of sterile water. Animal died Jan. 24, 1922. *Autopsy:* abdominal organs markedly tuberculous.

G. P. no. 18: Jan. 17, 1922. Injected intraäbdominally 0.5 cc. tuberculous emulsion, as in G. P. no. 16, and hypodermically 100 mgm. thorium nitrate in 1 cc. sterile water. Jan. 20, hypodermically, 200 mgm.; and Jan. 29, by mouth, 100 mgm. Jan. 30, animal had paralysis of the hind legs. The injections of the thorium nitrate were made on the outside of the hind legs. Animal died Jan. 31. *Autopsy:* Left hind leg, seat of injection of the thorium nitrate, soft and watery. Marked tuberculous lesions of viscera. Serous effusion in abdominal cavity; pleurisy with effusion.

G. P. no. 19: Jan. 17, 1922. Injected intraäbdominally 0.5 cc. tuberculous emulsion as in G. P. no. 16. Followed by 100 mgm. thorium nitrate in 1 cc. sterile water, intraäbdominally. Jan. 22, by mouth, 100 mgm. Animal died Feb. 5, 1922. *Autopsy:* Tuberculous infection in all viscera. Intestines matted together with adhesions. Seat of intraäbdominal injection of the 100 mgm. of radioactive salt is an abscess. Seat of injection of the 200 mgm. looks edematous.

G. P. no. 20: Jan. 17, 1922. Injected intraäbdominally 0.5 cc. tuberculous emulsion as in case no. 16. Followed by intraäbdominal injection of 100 mgm. thorium nitrate in 1 cc. sterile water. Jan. 18, 1922, found dead. *Autopsy:* Enteritis. Bloody fluid in peritoneal cavity.

G. P. no. 21: Jan. 17, 1922. In this case the tuberculous emulsion was exposed to the action of the radioactive salt before injecting it into the animal. This method is termed here "treated" emulsion. The concentration of the radioactive salt was 1 to 100. The dose of the emulsion was 0.5 cc., as in case no. 16. The time of exposure of the emulsion to the action with the solution of the radioactive salt was five minutes. This was injected intraäbdominally. Jan. 27, 100 mgm.; Jan. 29, 100 mgm.; Feb. 5, 100 mgm.; all by mouth. Feb. 8, found dead. *Autopsy:* Marked tuberculous lesions in omentum, liver and spleen. Spleen is about four times normal size.

G. P. no. 22: Jan. 21, 1922. One-half cubic centimetre of tuberculous emulsion, same as that used for control no. 16, was here "treated" with the radioactive salt; the concentration of the salt was 1 to 100; time not specified. Feb. 17, animal was found dead. *Autopsy:* Generalized tuberculosis of all viscera; abdominal effusion; pleurisy with effusion.

G. P. no. 23: Jan. 21, 1922. Injected intraäbdominally tuberculous emulsion, the same as that used for control no. 16. But, before injecting this dose, the emulsion was "treated" with the radioactive salt several days (Jan. 17 to Jan. 21). An abscess of the groin developed. Animal was chloroformed. *Autopsy:* The Lungs showed several tuberculous nodules. The liver and spleen were considerably enlarged.

The dose of the emulsion was then reduced to 0.2 cc. and the concentration of the radioactive salt was increased to 1 to 50 of water. This concentration acts best in an albuminoid medium.

G. P. no. 24: Feb. 4, 1922. Control to G. P. nos. 25 and 26. Injected intraäbdominally 0.2 cc. tuberculous emulsion of cow's udder. No treatment. Died April 15, 1922, of generalized tuberculosis of abdominal viscera and the lungs.

G. P. no. 25: Feb. 4, 1922. Injected intraäbdominally 0.2 cc. tuberculous emulsion, same as in G. P. no. 24, but this emulsion was "treated" previous to injection with a concentrated solution of thorium nitrate, namely, 1 to 50 of water, during a period of seven minutes. Feb. 26, 8 mgm.; March 3, 50 mgm.; March 8, 30 mgm.; March 11, 20 mgm.; March 13, 30 mgm.; March 21, 30 mgm.; March 25, 30 mgm.; March 26, 30 mgm.; March 28, 30 mgm.; March 30, 30 mgm.; April 2, 30 mgm.; April 4, 30 mgm.; all by mouth. Animal was chloroformed April 11. *Autopsy:* Small abscess at point of inoculation. Liver, spleen and abdominal glandular system infected with tuberculosis; all lobes of the lungs but two infected with tuberculosis.

G. P. no. 26: Feb. 4, 1922. Tuberculous emulsion, same as that used for control no. 24, "treated" previous to injection with thorium nitrate solution in concentration 1 to 50 of sterile water, during a period of 7 minutes. March 2, 25 mgm.; March 5, 50 mgm.; March 8, 30 mgm.; March 28, 30 mgm.; March 30, 30 mgm.; April 2, 30 mgm.; all by mouth. *Autopsy:* Generalized tuberculosis of the viscera; spleen almost black, about five times its normal size; liver considerably enlarged; lungs markedly infected with tuberculosis; tuberculous peritonitis.

G. P. no. 29: Feb. 8, 1922. Emulsion of tuberculous organs of G. P. no. 21 "treated" with thorium nitrate solution, concentration 1 to 50 of water, for 30 minutes. Intraäbdominal injection of this mixture made 0.5 cc. February 23, left testicle enlarged. March 3, 50 mgm.; March 6, 20 mgm.; March 8, 30 mgm.; March 11, 20 mgm.; all by mouth. March 15, animal was chloroformed. *Autopsy:* Marked tuberculosis of the liver, spleen, pancreas and lymph nodes. Lungs show hemorrhagic spots; testicle is the seat of an abscess.

G. P. no. 36: Feb. 20, 1922. Tuberculous emulsion from organs of G. P. no. 21, "treated" with thorium nitrate solution, concentration 1 to 50 of sterile water; this "treated" emulsion, 0.2 cc., injected intraäbdominally. March 6, 20 mgm.; March 8, 60 mgm.; March 11, 30 mgm.; March 13, 30 mgm.; March

17, 30 mgm.; March 19, 30 mgm.; March 21, 30 mgm.; March 25, 30 mgm.; March 26, 30 mgm.; March 30, 30 mgm.; April 2, 30 mgm.; April 4, 30 mgm.; April 7, 30 mgm.; April 18, 30 mgm.; April 24, 30 mgm.; all by mouth. Died May 4, 1922. *Autopsy:* Generalized tuberculosis. Liver and spleen are twice normal size. Lungs, lymph nodes and omentum infiltrated with tuberculosis. Spleen and liver markedly tuberculous. Peritoneal effusion.

G. P. no. 37: February 20, 1922. Injected intraäbdominally tuberculous emulsion from G. P. no. 2. Emulsion "treated" with thorium nitrate solution, concentrated 1 to 50 of sterile water; the solution of the radioactive salt and the tuberculous emulsion remained in mixture from Feb. 20 to 22. The animal was treated with thorium nitrate both by mouth and hypodermically. It was chloroformed June 9, 1922. *Autopsy:* Seat of inoculation is an abscess; spleen destroyed by tuberculosis; liver tuberculous; lungs infected with tuberculosis.

EXPERIMENTS WITH OXYGEN

I now had recourse to neutral treatment. I used oxygen as follows:

1. Twenty-five per cent of oxygen and 75 per cent of air, nine hours daily.

2. Fifty per cent of oxygen and 50 per cent of air, nine hours daily.

3. Pure oxygen, two hours daily. In some of these cases was added treatment with lipase or steapsin, by mouth and hypodermically; but the lipase or steapsin was not neutralized.

Apparatus for adninistering the oxygen: Prof. Arthur J. Franks designed a cabinet and helped me to install the necessary apparatus.

The cabinet: The cabinet, six inches deep, had two inlets for the mixed oxygen and air; on the opposite side to the inlets were two outlets. These inlets and outlets were made by drilling holes in the wood of the cabinet and sealing in glass tubes of appropriate diameter, for the purpose of connecting the inlet ends with the sources of supply of air and oxygen. A fifth opening was made in the cabinet, into which a glass tube was sealed in; this opening connected with a manometer; this was to guard against undue pressure inside the cabinet, while the compressed air and the oxygen were irrigating the cabinet. At the upper part of the cabinet and all around it was a trough for the purpose of holding mercury, about one inch deep. Through the bottom of this trough was drilled a hole, into which was inserted a glass tube with a stopcock; this was for draining the trough of the mercury when required. This tube was also sealed in. The cover of the cabinet was a wooden frame to which was fitted and sealed in a heavy plate of glass, through which

the animals could be observed. The frame was made so that it fitted into the trough full of mercury and, when put in, sealed the cabinet hermetically. The whole cabinet and frame were thoroughly paraffined two or three times. Inside the cabinet was placed a container, protected with wire netting; calcium chloride was in the container to absorb undue moisture when the animals were being treated there.

The oxygen was led from a cylinder under pressure into a calibrated flow-meter; a fine gauge adjustment helped to regulate and obtain the required flow. The compressed air was similarly led into a flow-meter so that the required amount of air was allowed to flow through. Both the oxygen and the air were then led into a Y-shaped tube, where they mixed, and were led into a container with concentrated sulphuric acid, to absorb any moisture in the gases. Broken pieces of fine glass tubing were at the bottom of this container to facilitate the process. From this container the mixed gases were led into another one, with glass beads and sodium hydroxide to absorb the CO_2 in the gases. From this container the gases were led into another Y-shaped tube; the two branches of this connected with the two inlets into the cabinet.

The following cases illustrate the results obtained:

OXYGEN TREATMENT; 25 PER CENT OXYGEN, 75 PER CENT AIR

G. P. no. 57: June 21, 1922. Injected intranasally 0.1 cc. tuberculous emulsion from tuberculous lymph node of a pig. Treated with oxygen, 25 per cent, air 75 per cent, in cabinet, nine hours daily. Died Aug. 23, 1922. *Autopsy:* Lungs destroyed by tuberculous degeneration. Liver, twice normal size, destroyed by tuberculous degeneration. Spleen enlarged and with disseminated tuberculosis.

G. P. no. 59: June 21, 1922. Injected into lungs, by way of nasal passages, 0.1 cc. tuberculous emulsion from lymph node of a pig. Treated animal with oxygen 25 per cent, air 75 per cent, in a cabinet, nine hours daily. Animal was chloroformed July 12, 1922. *Autopsy:* Marked tuberculous infection of lungs.

OXYGEN TREATMENT; 50 PER CENT OXYGEN, 50 PER CENT AIR

G. P. no. 58: June 21, 1922. Injected into lungs, by way of nasal passages, 1 cc. tuberculous emulsion from lymph gland of a pig. Treated animal with oxygen 50 per cent and air 50 per cent, nine hours daily. Animal was chloroformed July 10, 1922. *Autopsy:* Generalized tuberculosis of all pulmonary lobes.

OXYGEN TREATMENT; PURE OXYGEN, DAILY TWO HOURS

G. P. no. 68: July 12, 1922. Injected into lungs, by way of nasal passages, 0.1 cc. tuberculous emulsion from lungs of G. P. no. 60. Animal died August 13, 1922. *Autopsy:* Lungs tuberculous; liver and spleen degenerated with tuberculosis; each of the latter organs twice normal size.

All the cases treated with oxygen in the various concentrations died of tuberculosis. In some of these I added to the oxygen treatment chaulmoogra oil by mouth, one drop twice daily. It should be borne in mind that chaulmoogra oil contains fatty acids (17); besides, it is an irritant to the gastrointestinal tract. Many of the animals so treated showed gastroenteritis and *all of them died of generalized tuberculosis.*

Having disposed of this side of the problem definitely, I took it up anew from the viewpoint of waxes and their solubilities.

EXPERIMENTS WITH OXYGEN AND STEAPSIN

Dr. J. Lewkowitsch (18) and others class waxes with fats. Agents that dissolve fats are said to dissolve waxes. Steapsin or lipase hydrolyzes fats in the body. Steapsin or lipase is secreted by the pancreas. There are many other sources of lipase, but I obtained it from the pancreatic gland of cattle. I am indebted to Dr. W. E. Howe, Inspector in Charge of Field Office of the U. S. Bureau of Animal Industry, Denver, Colorado, for supplying me with the pancreatic glands required in this work.

Steapsin works best in an alkaline medium, according to Claude Bernard (19). Other physiologists make other claims. Without testing the steapsin as to its reaction after I obtained the extract, I began the treatment of the animals as follows: The extract was given by mouth, 1 cc., twice daily; the sterile filtrate was given hypodermically twice or three times a week; and the pure oxygen was administered two hours daily. The administration of the pure oxygen had to be interrupted frequently to relieve difficult breathing. After three months of this treatment a few of the animals were apparently cured of their tuberculous infection. This was the first time that I produced any apparent cure of tuberculosis in guinea pigs. But the percentage of these cases was small.

Examining the tuberculous lesions of the animals that died, I found that these lesions were rather mild as compared to those caused by the acid treatment with radioactive salts. The next step, then, was in the direction of increasing the saponifying effect of lipase.

The following cases illustrate the results obtained from treatment with pure oxygen and lipase without neutralizing it:

G. P. no. 49: Aug. 18, 1922. Injected into lungs, by way of nasal passages, tuberculous emulsion from G. P. no. 55. Treated animal with steapsin extract by mouth twice daily and hypodermically twice or three times a week. Pure oxygen daily during a period of two hours. Animal was always chloroformed or etherized before also injecting into lungs filtered steapsin occasionally. Animal died from effect of overdose of chloroform Nov. 25, 1922. *Autopsy:* Upper pulmonary lobes show tuberculous lesions; several small foci of tubercles in the other pulmonary lobes. One tuberculous focus, about 5 mm. in diameter, in spleen.

G. P. no. 78: Sept. 8, 1922. Injected into lungs, by way of nasal passages, 0.1 cc. tuberculous emulsion from lungs of G. P. no. 67. *Treatment:* Lipase without neutralizing it, by mouth and hypodermically; pure oxygen two hours daily. Animal died Dec. 2, 1922. *Autopsy:* Slightly pleuritic and peritoneal effusion. All the pulmonary lobes show miliary tuberculosis. Liver enlarged; slight disseminated tuberculosis; spleen slightly enlarged. The striking features in this case are the long period of illness and the slight tuberculous lesions compared to those in cases treated with radioactive salts.

G. P. no. 51: Aug. 14, 1922. Injected into lungs, by way of nasal passages, 0.2 cc. tuberculous emulsion from G. P. no. 55. Given extract of lipase twice daily, without neutralizing; hypodermically, the sterile filtrate, twice or three times a week; pure oxygen two hours daily. Occasionally injected into lungs filtrate, chloroforming animal before doing so. Animal died Nov. 8, 1922. *Autopsy:* Kidneys slightly congested; liver cuts hard; lungs in good condition; one white spot, size of about 2 mm. in diameter; smear of this shows no acid-fast rods present. Rupture of stomach; fairly marked enteritis. Both controls to this animal died of tuberculosis.

G. P. no. 70: Aug. 18, 1922. Injected into lungs 0.2 cc. tuberculous emulsion from G. P. no. 55. *Treatment:* extract of steapsin, without neutralizing it, by mouth twice daily; sterile filtrate, without neutralizing it, twice or three times a week; pure oxygen two hours daily. Animal had temperature varying between 101° and 102° until September 17, 1922, then it ran between 100° and 99°F. On October 29 it had a liter of four young: temperature then ranged between 102° and 101° until Dec. 7. Sodium bicarbonate and ox-bile salts (extracted from ox bile) were then added to the treatment. This animal made a good recovery; temperature ranged between 99° and 98°; this animal and the female of the litter were given away; six months later both were in good condition.

A few other animals similarly treated also recovered from the infection. Their control, G. P. no. 72, died of generalized tuberculosis, September 26, 1922.

Method of preparing lipase or *steapsin:* Lipase or steapsin may be obtained from various sources. When obtained from the pancreatic gland the latter must be procured from a freshly killed animal; the extract must be made as soon as possible thereafter; otherwise the lipase content is either markedly reduced or completely destroyed. I use lean glands to avoid an excess of formation of fatty acids by the action of the lipase on the fat of the gland itself. The gland is stripped of its connective tissue and fat as much as possible. It is best to use rubber gloves, sterilized, if possible, to handle the gland. This answers a double purpose, that of cleanliness as well as preventing the hands from getting "rough" through the action of the steapsin on the fatty matter of the hands. When stripped of the connective tissue and fat, the gland is weighed, cut into small pieces and put into a porcelain mortar. Clean, sterilized sea-sand is put on the bottom of the mortar and on top of the cut pieces of the gland. The mass is reduced to a uniform pulp by crushing with the pestle. Pure glycerol, as fresh and free from moisture as possible, is now added to this pulp. The proportion of the glycerol that insures a sterile extract is probably ten times the weight of the gland used; but I used only five times the weight in order to obtain a more concentrated extract. The mixture is now poured into a sterile stained glass container; light decomposes or destroys the steapsin; the container is well stoppered to keep out air and moisture; a clean, stout paper napkin or layers of cheese cloth may be put over the stopper and held in place with a rubber band. I prefer a wide-mouthed container; it is easier to pour into it the material and easier to clean if the mouth of the container admits one's hand. The mixture should be kept in a cool place. I have not yet decided whether too much chilling is injurious to the lipase. I have kept the product in a cool room in the winter; in summer I wrap the container in a towel, fasten the towel around it, put it into a dish containing some water so that the towel is always wet, and evaporation of the water from the towel keeps the contents cool. The extract is at its best when allowed to stand two weeks before using it. It can be kept a long time without deteriorating; I have an extract made April, 1923; it is still effective and sterile.

Filtrate for hypodermic use: For hypodermic use the extract is filtered to render it sterile. Both a Mandler and a Berkefeld filter answer the purpose. The extract itself is too thick to filter and it should be diluted with distilled water, half and half, although a stronger concentration can also be obtained. The filtrate is always examined bacteriologically before using.

As the lipase is injured by light I wrap the whole filtering apparatus in heavy, clean, paper napkins; the filtering room is kept dark and cool, summer and winter. Water or air suction may be used for this filtration.

The filtrate of the first and even of the second day is poor in lipase, since the porcelain filter adsorbs it. This first filtrate is taken out, but may be used as water to dilute the extract for filtration.

Acidity of the pancreas, the extract and the filtrate: When I began to use the steapsin, I took it for granted that the extract and the filtrate were alkaline, and I thought that the animals were getting alkaline treatment. But when I found that only a very few of the animals had been apparently cured of the tuberculous infection I tested the reaction of the gland tissue and found it acid to litmus. I also found the reaction of the extract of the gland and that of the sterile filtrate acid to litmus. But when I tested the reaction of the mixture of the pulp of the gland and the glycerol, immediately after mixing with glycerol, the reaction was neutral or alkaline. This reaction seemed to indicate the following: The steapsin acts on the fat of the gland itself as soon as the animal is killed; the admixture of glycerol renders the material neutral or alkaline; but, on standing, the lipase probably renews its activity and again hydrolyzes the fat in the mixture and liberates fatty acids once more. It was clear then that when alkaline treatment is desired the extract and the sterile filtrate must be rendered alkaline. I then understood more clearly Claude Bernard's remark that steapsin works best in an alkaline medium.

ALKALINE MEDIUM FOR STEAPSIN. THE PREFERRED ALKALINE SALT TO BE USED. HYDROLIZING BEE'S WAX. HYDROLYZING THE COATING OF THE TUBERCLE BACILLUS. INSULIN VERSUS STEAPSIN. ACTION OF LIPASE BY CONTACT. CHLOROFORM AS A COHYDROLYZER

I used sodium bicarbonate or potassium bicarbonate for rendering the steapsin alkaline. It is preferable to use the potassium salt. Lew-

kowitsch (20) and other chemists state that when a glyceride or a fat is hydrolyzed with potassium hydroxide a soft soap is formed, whereas a hard soap is formed when sodium hydroxide is used as a hydrolyzer. While testing the hydrolyzing effect of alkaline steapsin on bee's wax I found this agent insufficient. It occurred to me that by adding a small proportion of a strong hydrolyzer of wax I could possibly also make use of it as a hydrolyzer or decorticator of the tubercle bacillus. I tried various hydrolyzers, such as carbon tetrachloride, kerosene oil, ethyl ether, chloroform, etc. Chloroform became my choice cohydrolyzer. Having determined the smallest amount of chloroform as a useful cohydrolyzer to be two drops per cubic centimetre of the sterile filtrate of lipase, I proceeded to use it for the treatment of guinea pigs. As I was also using insulin as a decorticator of the tubercle bacillus, the insulin was also rendered alkaline, mixed with the chloroform and tested as a hydrolyzer of bee's wax as well as an agent to decorticate the tubercle bacillus in the living body.

Chemical test of bee's wax. The method of judging the effect of a hydrolyzer of bee's wax is based here on the amount of fatty acids liberated by the chosen hydrolyzer. In these chemical tests, Mr. R. A. Baxter, Instructor in Chemistry, helped me to make the titrations of the fatty acids liberated by the lipase and insulin, respectively. I am indebted to Dr. John G. Ryan, Denver, Colorado, for his courtesy in obtaining for me the insulin.

The dose of insulin chosen for the tests was advisedly small; as hypodermic injections with steapsin mixture were being made twice and even three times a week, it was judged that the insulin injections, substitutes for steapsin, would have to be made as often. The concentration of the insulin used was as follows:

Five-tenths of a cubic centimetre, which equals five units of insulin for man, was mixed with sterile water enough to make 100 cc. This solution made up 500 units for a guinea pig, or 0.2 cc. of the solution represented one unit for a guinea pig. This unit was chosen on the assumption that the weight of a medium sized guinea pig is one-hundredth the weight of man. To indicate this chosen solution it is designated in this paper as *insulin 1/100*.

Rough tests were made on bee's wax to find the comparative solvent or saponifying effect of insulin of the above mentioned solution, of unfiltered and of filtered lipase or steapsin. It should be borne in mind

that filtered steapsin or lipase is diluted unfiltered lipase and that, as has been mentioned, the dilution is made with water in order to make the extract filterable.

The tests were made as follows:

1. 10 mgm. bee's wax
   1 cc. unfiltered lipase
   1 cc. water
   4 drops chloroform
   10 mgm. potassium bicarbonate

2. 10 mgm. bee's wax
   2 cc. filtered lipase
   4 drops chloroform
   10 mgm. potassium bicarbonate

3. 10 mgm. bee's wax
   0.2 cc. insulin solution, 1/100 1.8 cc water added to make up 2 cc.
   4 drops chloroform
   10 mgm. potassium bicarbonate

There was an appreciable softening of the wax after three minutes at room temperature, about 19° to 20°C., but when warmed to body temperature, about 37°C., the wax was well softened in all the specimens after the fifth minute.

A test was then made to determine the actual solvent or saponifying effect of insulin, unfiltered lipase and filtered lipase respectively, the test being judged by the amount of fatty acids liberated.

It was pointed out in another paper that the best results were obtained with steapsin when mixed with chloroform, ethyl ether, carbon tetrachloride or with other suitable cohydrolyzers in minute doses, but preferably with chloroform, and some harmless alkaline agent such as sodium carbonate or bicarbonate, potassium carbonate or bicarbonate. As chloroform alone is an energetic solvent of bee's wax it was considered interesting to test its effect when mixed with water, with insulin, with unfiltered and with filtered lipase. As it was sought to find out the saponifying effect by the amount of fatty acids liberated, the alkaline agent was left out of the mixture; this allowed the titration of the fatty acids to be made by means of sodium hydroxide solution. The following tests illustrate the method of procedure:

100 mgm. bee's wax
10 cc. distilled water
20 drops chloroform

The water alone required 0.95 cc. N/1000 sodium hydroxide to be neutralized. The acidity in this mixture was neutralized with 1.75 cc. N/1000 sodium

hydroxide; subtracting 0.95 leaves 0.80 cc. sodium hydroxide required to neutralize the fatty acids liberated.

The distinguishing feature of bee's wax in such a mixture is that the wax does not disintegrate; no particles of the wax float in the water or render it cloudy. The wax acted upon by the chloroform in the water is apparently not soluble in the water; the wax holds together in a mass that does not smear on the wet surface of the test tube.

The solution of insulin used in the concentration indicated was neutral to phenolphthalein.

100 mgm. bee's wax
10 cc. insulin, full strength of the solution
20 drops chloroform.

Neutralized with 2.3 cc. N/1000 sodium hydroxide.

100 mgm. bee's wax
10 cc. unfiltered lipase
20 drops chloroform.

The extract of lipase alone was neutralized with 245 cc. N/1000 sodium hydroxide; and the mixture was neutralized with 248 cc. N/1000 sodium hydroxide; substracting leaves 3 cc.

As has been stated, the extract of steapsin becomes acid shortly after the glycerol is mixed with it. Presumably the lipase acts on the fatty matter of the gland itself, liberating fatty acids.

The filtered lipase is a diluted extract of unfiltered lipase. The filtered lipase required 66.76 cc. N/1000 sodium hydroxide to be neutralized. The test was then made as follows:

100 mgm. bee's wax
10 cc. filtered lipase
20 drops chloroform.

After shaking the mixture five minutes and stirring it with a glass rod, the mixture was neutralized with 79.50 cc. N/1000 sodium hydroxide. Subtracting 66.76 cc. leaves 12.74 cc. required to neutralize the fatty acids liberated by the filtered steapsin mixture.

These tests seem to indicate the progressively increasing amounts of fatty acids liberated from bee's wax as follows:

Acids liberated from chloroform in water were neutralized with 0.80 cc. N/1000 sodium hydroxide.

Acids liberated with insulin, 1/100, and chloroform, were neutralized with 2.3 cc. N/1000 sodium hydroxide.

Acids liberated with the extract or unfiltered steapsin and chloroform were neutralized with 3 cc. N/1000 sodium hydroxide.

Acids liberated with filtered steapsin and chloroform required 12.74 cc. N/1000 sodium hydroxide.

From these tests it is seen that the dilution of insulin used in the mixture does not act as energetically as does the diluted and filtered steapsin.

The wax used in the above experiments had been lying around in the laboratory about two years, unprotected against moisture of the air. Bee's wax protected against such moisture by inclusion in paraffin was then tested. Of course, the protecting layer of paraffin was thoroughly shaved off. The results obtained are given below. In each test the mixture with the bee's wax was allowed to stand one hour and forty-five minutes:

100 mgm. bee's wax
10 cc. insulin, 1/100, full strength of the solution
20 drops chloroform

It took 3.25 cc. N/1000 sodium hydroxide to neutralize the fatty acids liberated. The blank test of this insulin required 1.05 cc. N/1000 sodium hydroxide; subtracting, leaves 2.2 cc.

100 mgm. bee's wax
10 cc. filtered steapsin or lipase
20 drops chloroform

It took 171.2 cc. N/1000 sodium hydroxide to neutralize the fatty acids liberated. The blank steapsin filtrate required 109.3 cc. N/1000 sodium hydroxide to be neutralized; subtracting, leaves 61.9 cc.

The above figures seem to indicate that the filtered steapsin is more effective as a cohydrolyzer of bee's wax than is insulin in the dilutions used. These chemical tests seem to parallel the microchemical tests presented below, which seem to indicate that filtered steapsin is a better decorticator of tubercle bacilli, in a given period of time, than is insulin when each is used in the mixture indicated.

It should be borne in mind that the effectiveness of the steapsin as a cohydrolyzer depends on many conditions, some of which are the source

from which the steapsin is obtained, the concentration of the extract, the age of the filtrate, the method of obtaining the filtrate, etc. Further studies are needed to standardize the cohydrolyzing effect of steapsin when used as a decorticator of tubercle bacilli.

Testing decortication or solubility of tubercle bacilli, virulent bovine and human types. Liquid rich in bacilli; not less than fifty acid-fast rods per field. Insulin and filtered steapsin as respective hydrolyzers: According to the chemical tests presented above, it seems that the steapsin extract is a better hydrolyzer of bee's wax than is insulin, in the concentrations and mixtures used. Dr. Stiles and I now tested the same mixtures as hydrolyzers or decorticators of the tubercle bacillus. The cultures of the tubercle bacilli were obtained from Dr. G. W. McCoy, Director, Hygienic Laboratory, U. S. Public Health Service, Washington, D. C., to whom we are indebted for this courtesy.

Method of testing the hydrolyzing effect: A small, sterile, Erlenmeyer flask, with sterile glass beads, was used as a container. Into this container were poured, with a sterile pipette, the suspension of the tubercle bacilli, the filtered steapsin or the insulin, according to which was being tested as a hydrolyzer, enough sterile bicarbonate or carbonate of potassium to render the mixture alkaline, and two drops of chemically pure chloroform to each cubic centimetre of the liquid used. In some cases sterile water was used instead of either the steapsin or the insulin; this was done in order to test whether the two drops of chloroform in the mixture were alone responsible for the hydrolyzing effect on the tubercle bacillus. In other cases the alkaline salt was not used; this was done in order to ascertain whether this alkalinity had anything to do with the disappearance of the acid-fast stain of the tubercle bacillus. In each case the ingredients used are given in the tests. In each case five minutes were consumed in shaking up the contents in the flask. It is well to remark, however, that usually four flasks were being prepared for the test; the time factor is of importance in the process of decortication; it was physically impossible, under the circumstances, to have each one of the four flasks and its contents exposed to the effect of the mixture only five minutes: the time required in pouring the ingredients into each of the four flasks made the difference in time; when eight flasks were used a longer time factor was involved.

The following tests speak for themselves:

1
- 1 cc. suspension tubercle bacilli
- 1 cc. distilled water
- 4 drops chloroform

Result: Numerous acid-fast rods present

2
- 1 cc. suspension tubercle bacilli
- 1 cc. distilled water
- 4 drops chloroform

Result: Acid-fast rods present

3
- 1 cc. suspension virulent tubercle bacilli
- 1 cc. filtered steapsin
- 4 drops chloroform

Result: No acid-fast rods observed

4
- 1 cc. suspension tubercle bacilli
- 1 cc. insulin, 1/100
- 4 drops chloroform

Result: Numerous acid-fast rods present

Tests 1 and 2 show that when water was substituted for steapsin or insulin the four drops of chloroform did not defat the tubercle bacillus. Tests 3 and 4 show that when the alkaline salts are left out of the mixture, the steapsin, even then, is a better hydrolyzing agent than is insulin, in the dilutions used.

5
- 1 cc. suspension tubercle bacilli
- 1 cc. filtered steapsin

Result: Dr. Stiles said, "I recognize rods similar to tubercle bacilli, but the red stain is lost."

6
- 1 cc. suspension tubercle bacilli
- 1 cc. insulin 1/100

Result: Numerous acid-fast rods

Tests 5 and 6, in which only steapsin and insulin were used, again show the superiority of steapsin as a hydrolyzer. It is well to remark that these tests are picked out as types; but they are not always found invariable, for the time factor probably enters into the reaction. We made several

hundred tests and the typical ones only are shown here. In the following three tests, a comparison is made between water, insulin 1/100 and steapsin, when chloroform is left out of the mixture:

7 { 1 cc. tubercle bacilli
1 cc. distilled water
10 mgm. potassium bicarbonate

Result: Acid-fast rods present

8 { 1 cc. tubercle bacilli
1 cc. filtered steapsin
10 mgm. potassium bicarbonate

Result: No acid-fast rods present

9 { 1 cc. tubercle bacilli
1 cc. insulin 1/100
10 mgm. potassium bicarbonate

Result: Acid-fast rods present

These tests, 7, 8 and 9, again show the better hydrolyzing power of steapsin over insulin in the dilutions used.

In the following tests all the ingredients were used, except where distilled water also figures as an ingredient:

10 { 1 cc. tubercle bacilli
1 cc. insulin 1/100
10 mgm. potassium bicarbonate
4 drops chloroform

Result: No acid-fast rods observed

11 { 1 cc. tubercle bacilli
1 cc. filtered steapsin
10 mgm. potassium bicarbonate
4 drops chloroform

Result: No acid-fast rods

12 { 1 cc. tubercle bacilli
1 cc. distilled water
10 mgm. potassium bicarbonate
4 drops chloroform

Result: Numerous acid-fast rods

13
- 1 cc. tubercle bacilli
- 1 cc. insulin 1/100
- 10 mgm. potassium bicarbonate
- 4 drops chloroform

Result: Numerous acid-fast rods

14
- 1 cc. tubercle bacilli
- 1 cc. filtered steapsin
- 10 mgm. potassium bicarbonate
- 4 drops chloroform

Result: No acid-fast rods observed

15
- 1 cc. tubercle bacilli
- 1 cc. insulin 1/100
- 10 mgm. potassium bicarbonate
- 4 drops chloroform

Result: Acid-fast rods present

16
- 1 cc. tubercle bacilli
- 1 cc. filtered steapsin
- 10 mgm. potassium bicarbonate
- 4 drops chloroform

Result: No acid-fast rods present

Again we see in the above tests that the steapsin filtrate seems to be the more reliable hydrolyzer as compared with insulin, in the dilutions used. But when sufficient time is allowed the insulin mixture, with all the ingredients present, it also decorticates the tubercle bacillus. We have used the insulin mixture on highly concentrated suspensions of bovine as well as human tubercle bacilli, showing about one hundred acid-fast rods per field; when the mixture was agitated for a period of from one to two hours no acid-fast rods could be found under the microscope. Tubercle bacilli so treated, either with the steapsin or the insulin mixture, freed of the unnecessary organic matter and the chloroform, were used as a *bacterin*. Many animals were injected with such treated tubercle bacilli, with results that are, to date, promising and which will be reported later.

The microchemical tests cited above show definitely that both the steapsin and the insulin mixtures decorticate the tubercle bacillus by actual *contact* with the microörganism. It has already been pointed out,

and it is well to repeat, that "the waxes are decomposed by saponification into fatty acids and the higher alcohols . . . . the difficulty met with in the saponification of waxes is no doubt due to the fact that the soaps formed are less readily soluble than those usually obtained on saponifying fats . . . . Such soaps would naturally envelop unsaponified wax, thus protecting it from contact with alkali" (21).

What is said about saponified wax seemed to me to apply also to the tubercle bacillus. In the last cases cited above I was led to believe that I could obtain a larger percentage of cures by rendering the steapsin alkaline. The microchemical tests supported this view definitely. But it seemed also clear to me that the curative mixture used must be most effective when coursing through the circulation and the lymphatics, where it comes in actual contact with the tubercle bacilli. Consequently, I reasoned that where such contact was not possible by reason of the formation of insoluble salts that would envelop unsaponified tubercle bacilli, thus protecting them from contact with the mixture, as is explained by Dr. Lewkowitsch, an adjunct treatment was necessary. I chose *pure* ozone as such an adjunct treatment.

The results thus obtained with *pure* ozone have been so encouraging that I have sought to simplify the method by using a substitute,—that of activated oxygen, as obtained from calcium hypochlorite, or an iodine substitute for the chlorine. These experiments with lipase mixture and the adjunct treatment, *pure* ozone or a substitute thereof, have progressed far enough to justify their repetition on a large scale in order to gain cumulative evidence. Their results will be presented later.

CONCLUSIONS

1. Chemically speaking, diseases caused by microörganisms may be grouped into two classes: (1) diseases amenable to acid treatment and (2) diseases not amenable to acid treatment.

2. An acid medium apparently favors the growth of the tubercle bacillus.

3. An alkaline medium seems to be unfavorable to this bacillus.

4. Steapsin or lipase, alkalinized and mixed with a strong cohydrolyzer of wax, decorticates the tubercle bacillus.

5. An insulin mixture, similar to the lipase mixture, also decorticates the tubercle bacillus.

6. On the basis of these findings, and proceeding on the assumption that there might be devised a therapeutic measure in which some adjunct were used to render tubercle bacilli in the animal body open to the destructive action of steapsin and insulin, further experiments are in progress in which ozone and activated oxygen (obtained from calcium hypochlorite) are being used as the adjuncts.

7. Therapeutic experiments are also under way in which tubercle bacilli, subjected to the decorticating action of steapsin and insulin, with chloroform as a cohydrolyzer, are being used as a bacterin.

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